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# THE MEDICAL CLINICS of NORTH AMERICA

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## *SYMPOSIUM ON SPECIFIC METHODS OF TREATMENT*

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### NUTRITION IN PROTRACTED DISEASE

FREDRICK J. STARE, PH.D. M.D.\* GEORGE V. MANN, D.Sc. M.D.†  
ELIZABETH K. CASO, M.S.‡

FROM the strictly scientific viewpoint little is known about the effect of any of the chronic or protracted diseases on nutritional requirements. Certainly in protracted disease accompanied by fever, wasting or diarrhea nutritional requirements are increased, but just how much and for what specific nutrients is uncertain. The broad and practical aspects of human nutrition and disease are at last being approached experimentally, with the techniques and observations of experimental nutrition in the lower animals, useful additions to our understanding and therapy of many diseases appear probable.

There is no doubt of the vital importance of nutrition in combating protracted disease. It is ultimately a failure in cellular nutrition which will lead to tissue failure, organ failure and eventually to death. The food one absorbs is next to the oxygen one breathes, the most important continuous element of survival and health or disease is greatly influenced by the character and quality of this essential

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Fortunately, the body can "live off itself," except for water and oxygen, for varying periods of time, and hence the maintenance of good nutrition does not pose such formidable problems in acute illness of short duration. In chronic or protracted disease, however, the body may reach a stage where proper nourishment means the difference between further decline and death or convalescence and health. Unfortunately, it is frequently impossible to supply good nutrition, particularly to get it to the cells.

### FOOD IN NUTRITION

The physician's goal in nutritional therapy, or even nutritional advice, should always be to encourage the individual to consume a well balanced, varied diet of wholesome food, in sufficient quantity to furnish what is thought to be an adequate supply of nutrients and yet not be excessive in calories. Good nutrition over any length of time can come only from food, and variety in the selection of food is probably the single best thought to try to get across to the individual seeking or needing nutritional advice. Variety in choice of food coupled with an understanding of the importance of ideal body weight will generally result in good nutrition for patients who do not present serious disorders of appetite. Many common medical problems, as for example chronic nephritis, chronic liver disease and chronic infections such as tuberculosis or osteomyelitis, in which diet is of utmost importance to the outcome, can only be treated optimally when an adequate nutrient intake is assured. The following foods, if consumed daily, serve as a model list to supply good nutrition.

Milk or milk products	Fruits including citrus
Eggs	Butter or margarine
Meat, fish or poultry	Potatoes
Vegetables including leafy green or yellow	Breads and cereals—enriched or whole grain

The quantities of these foods to be consumed are important and will vary greatly among patients depending on a number of factors, principally appetite. Ideally, one would hope to have the patient consume daily a pint of milk or its equivalent, one egg, 4 ounces of meat, fish, or poultry, two servings\* of vegetables, one of which is green or yellow, and two servings\* of fruits, one of which is citrus. Calories to reach or maintain ideal body weight will be adjusted largely by varying the intake of bread and cereals, potatoes and fat.

Numerous substitutions of equivalent nutritional value are available for many of these foods, so that different pocketbooks and food habits may be satisfied. Thus milk products (cheese, ice cream, or the

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\* One serving equals  $1\frac{1}{2}$  cup

use of milk in cooking) will be equivalent to fluid milk. Peas, beans and oatmeal are good sources of protein in place of meat. Fish or fowl, tomatoes and raw cabbage will furnish ascorbic acid in place of citrus fruits.

In the individual with chronic disease the problem is more often one of insuring consumption of the nutrients represented by the above daily list of foods. This usually means more frequent feedings, special catering to food tastes, regularity of meal schedules, supplementing the diet with various nutritional concentrates, tube feedings, parenteral feedings or more likely a combination of these methods. It seems trivial to add that it is only the food that is consumed that can possibly be of any aid to the patient, yet many physicians feel that if good food is ordered nutrition is well taken care of.

Consumption of food by the chronically sick individual can frequently be increased by such simple procedures as offering six small meals a day rather than the conventional three and taking some care to see that the meals are attractive to the eye. Psychologically, large messy servings are often revolting not only to the sick but to the well. Recognizing that anorexia will reduce eating from a pleasure to a chore—and often an unpleasant one—less difficulty and less risk of nausea will be encountered with small feedings. To provide frequent attractive and nutritious servings takes only good food and well trained and sufficient help: enough dietitians, enough maids and enough kitchen help. Unfortunately many hospitals fall far short of these requirements. Lack of funds and rising costs of food and labor have not aided this condition but fundamentally it is due to a lack of interest on the part of physicians in insisting that their patients receive good nutrition. In this respect the physician who treats the patient in the home may have an advantage. The legerdemain of grandmother's cooking on doubtful appetites is well known.

Another essential to nutritional therapy may involve a change in the point of view of many physicians. Diet management which includes both additions as well as restrictions of nutrients, must be considered as an integral part of medical therapy. As such the diet prescription must be presented to the patient with the same insistence and authority as a prescription for any other medication. Most physicians are well aware of the masochistic traits of many patients who seem to relish a distasteful therapy when they believe that they will be helped by these discomforts. In diet therapy this and every other possibility will often be necessary to accomplish optimal nutrition and of considerable importance is the interest in and insistence on the part of the physician on good nutrition.

## NUTRITIONAL SUPPLEMENTS

Nutritional supplements most commonly used are concentrates of vitamins or protein and for individuals who are much below weight, concentrates rich in calories

**Vitamins**—Vitamin medication is prescribed when the patient's present intake of these nutrients is below recommended levels, when the diet in the past has been inadequate, or when there is a question of poor absorption due to diarrhea and other conditions. The dosages of vitamins are more or less empirical. The dietary recommendations of the Food and Nutrition Board of the National Research Council<sup>1</sup> are generally used as a basic standard for supplementary levels. When supplementation of the diet with vitamins is done on a therapeutic level, approximately five to ten times the National Research Council recommendations are generally used for the specific vitamins in which the individual is thought to be deficient, with levels of one to five times for the other vitamins. Most of the low cost, low potency, commercial vitamin preparations can be used for such purposes. These quantities for an adult for one day are as follows

	<i>National Research Council Recommended Daily Allowance</i>	<i>Therapeutic Level</i>
Vitamin A	5000 I U	25 000 to 50 000 I U
Vitamin D	—	1000 to 8000 I U
Thiamine	1.5 mg	5 to 20 mg
Riboflavin	1.8 mg	5 to 20 mg
Niacin	15.0 mg	75 to 300 mg
Ascorbic acid	75.0 mg	300 to 1000 mg

**Protein Preparations**—Protein supplements are likewise on an empirical basis. The quantity to be prescribed, and its effectiveness, will depend on the caloric needs and intake of the individual. If the caloric intake is below maintenance level, a certain amount of the protein will be used for energy purposes rather than nitrogen needs. Using protein supplements one should attempt to provide a minimum of 25 gm of protein per day and frequently amounts as high as 100 to 150 gm as in the case of patients with chronic liver disease or when there is a large protein loss, e.g., with massive proteinuria or when large amounts of protein are lost in serous or purulent effusions. In any event, supplementation should raise the total protein intake to that recommended by the National Research Council of 70 gm per day for the average adult male.

A variety of protein concentrates are available commercially for supplementation. They vary in the quantity of protein contained

Hydrolyzed protein preparations are also available for oral use although, except in the case of disease that may interfere with the production of digestive enzymes, there seems little justification for their use. The taste of protein hydrolysates is generally offensive and the price is much higher than unhydrolyzed protein preparations.

Not all protein preparations commercially available are of equal nutritive value. A recent study by Cannon and co-workers<sup>2</sup> has emphasized this fact. Milk powder is a good practical protein supplement averaging about 35 per cent protein. Many of the commercial protein preparations contain casein and lactalbumin as the protein base and are fortified with B-complex vitamins and occasionally yeast and liver. Somagen\* is an example of the latter and contains 70 per cent protein.

Protein supplements may be given in a variety of ways as between meal nourishments mixed with water, milk, or fruit juice or incorporated into prepared dishes particularly cooked cereals, cream soups and baked products. Adequate and creative dietary help is the single most important factor in insuring consumption.

**Supplementary Food**—Nutritional supplements of food other than vitamin or protein preparations are frequently of value, particularly when there has been considerable weight loss. Here it is largely a question of additional feedings: extra calories from a between meal glass of half milk and cream or a Dagwood sandwich at midafternoon or before bedtime.

The importance of regular meal habits in encouraging the appetite must be emphasized. In tuberculosis sanatoria where diet ranks with rest as a form of therapy the striking effect of meal punctuality upon appetites has often been noted. Intermediate meals when used as in the six meal schedule should be small and care must be taken that they do not interfere with the appetite for the following meal. A mid-afternoon feeding which causes the patient to refuse the evening meal will defeat the entire purpose. In intermediate feedings high fat levels may have to be avoided. Many patients will be able to take intermediate feedings only as fruit juices with perhaps some added carbohydrate or protein.

### TUBE FEEDING

Tube feedings are simply a means to an end: neither the patient nor the person who administers the tube feeding enjoys them. But in the individuals who cannot or will not eat by mouth tube feeding is to be preferred to parenteral feeding because better nutrition can thereby be furnished. Tube feeding formulas can vary from a simple mixture

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\* The Upjohn Company



of milk powder and water to complicated mixtures containing liver and many other foods that can be ground finely enough to pass through the tube.

Tube feeding formulas may be varied according to the caloric needs of the patient. The volume which can be tolerated also affects the concentration and composition of the formula. Milk products, eggs, various types of concentrated carbohydrates as sucrose, glucose and karo syrup, and vitamin and protein supplements are the basic ingredients for most tube feedings. Table 1 gives a simple tube feeding formula made of readily available foods. A simpler tube feeding formula, but more expensive, can readily be devised by using milk and cream with additions of one of the many commercially available nutritional supplements rich in protein, minerals and vitamins.

Abdominal distention and diarrhea are common complications of tube feeding. They can be minimized by small frequent feedings, care not to force air down the tube at the beginning of the feeding, and the use of pectin preparations or paeoric to control diarrhea. Tubes are generally more comfortable if put through a nostril rather than the mouth. They may be left down the same nostril for periods of a week. Tube feeding may be contraindicated in the presence of esophageal varices. Frequently the possibility of tube feeding or its use for a day or so may induce certain patients to force themselves to consume food by ordinary means. Although the procedure should not be presented as a punitive measure, the decision will finally be determined by the patient.

#### PARENTERAL FEEDING

Parenteral nutrition is required by those individuals who cannot or should not consume food by mouth. It is not possible today to provide good nutrition by vein. The seriousness of this situation to the individual patient will depend upon his present nutritional and physical status and the length of time complete parenteral nutrition is required. The greatest single handicap in parenteral nutrition is an inability to provide sufficient calories. Obviously this does not apply to the well nourished or obese individual in the usual period that parenteral nutrition is generally required. Adequate electrolyte therapy is also a phase of parenteral nutrition in which much more information is needed and to which some current research is devoted. Sufficient calories in parenteral nutrition are necessary to prevent extreme wasting of body tissues and to see that protein given by vein is adequate for nitrogen needs and not diverted to energy purposes. In the emaciated individual calories are needed to "put on weight." Blood,

TABLE 1

## TUBE FEEDING FORMULA

(Total volume, approximately 1 quart)

Food	Weight (gm)	Measure	Composition										
			Protein (gm)	Carbo- hydrate (gm)	Fat (gm)	Cal.	Ca. (gm)	Fe (mg)	Vit A (IU)	Thi- amine (mg)	Ribo- flavin (mg)	Niacin (mg)	Ascor- bic Acid (mg)
Milk evaporated	410	1 can	28.8	40.7	32.5	571	1.00	0.62	1600	0.2	1.5	0.8	5
Eggs	150	3	19.2	1.2	17.4	237	0.08	4.20	1700	0.18	0.5	0.2	
Cream, 20%	480	2 cups	11.6	16.0	80.0	832	0.39	0.24	3300	0.12	0.6	0.4	4
Sucrose	100	3 1/2 oz.		100.0		400							
Milk powder skim	90	3 oz.	30.3	44.1	0.9	306	1.10	0.48	30	0.3	1.7	0.9	6
Total			89.9	202.0	130.8	2346	2.60	5.54	6600	0.80	4.3	2.3	15

• Additional iron and vitamins can readily be added to the mixture from a variety of available preparations

glucose, saline, and various protein and vitamin preparations are about all that are available in a practical way for parenteral nutrition. Glucose solutions for intravenous use are seldom used in more than 10 per cent concentration for any length of time. Even in this concentration they are hypertonic, irritating to the vein wall, and frequently cause sclerosis of the veins. Depending on the concentration of the infusion solution and the rate at which it is infused, the kidney excretes a variable amount of sugar. These factors are increased with higher concentrations of glucose and more rapid rates of infusion.

Protein hydrolysates for infusion are usually used in a concentration of 5 per cent. The excretion of amino nitrogen from such preparations depends largely on how fast they are infused, but evidence indicates that with conventional infusion rates of 2 to 3 ml. per minute, 35 to 45 per cent of the infused nitrogen will promptly appear in the urine.<sup>3</sup>

A liter of 10 per cent glucose furnishes 400 calories if none of it is excreted. A liter of 5 per cent glucose or protein hydrolysate furnishes half this number of calories. Thus, it is evident that the question of fluid volume is an important one in parenteral feeding. Few adults can tolerate more than 4 to 5 liters of fluid by vein per day over any length of time. In addition there is the technical problem of supervising long intravenous infusions and the unpleasant task for the patient to lie quietly for this length of time, over repeated days, with a needle in his vein. Thus, the problem of supplying more than 1500 calories per day by vein without "drowning the patient" is evident. This will be solved when it is possible to give fat emulsions by vein. The desirability of fat for parenteral nutrition is clear since it would give a means of providing a high caloric intake with a minimum of fluid volume. With a sufficiently high caloric intake, the utilization of protein from parenteral or oral sources would be maximal, the destruction of body protein as a result of a caloric deficit would be minimal, and it ought to be possible to improve considerably the nutritional status of an undernourished individual.

Experimentally, fat preparations suitable for intravenous nutrition in the dog have been devised.<sup>4</sup> These have varied from 15 to 30 per cent in fat content, thus furnishing from 1500 to 3000 calories per liter—quite a difference from 200 or 400 calories as furnished by 5 or 10 per cent glucose.

The water soluble vitamins can be given by vein and a variety of suitable preparations are available. However, fat-soluble vitamin preparations for parenteral administration are not commonly available. Preparations of the latter would be useful in chronically ill patients who have had poor appetites, impairment of absorption from

the gastrointestinal tract or who are nauseated by the aftertaste of fish liver oils

A daily parenteral nutrition mixture that has been found useful is the following

Glucose 10 per cent solution	2000 ml	800 cal
Amigen* 5 per cent solution	1000 ml	200 cal
	and 50 gm of protein	
Solu B† with ascorbic acid	1 vial	
thiamine 10 mg		
riboflavin 10 mg		
nicotinamide 250 mg		
ascorbic acid 500 mg		
Saline 0.9 per cent	500 ml.	

### SODIUM RESTRICTION

Although emphasis in this paper has been given to nutritional supplementation as a method of diet therapy it must be remembered that in many diseases nutritional restriction of certain ingredients of the diet is just as necessary. Nutritional therapy is concerned with modifications of the nutritional intake whether by supplementation or restriction.

The introduction of sodium restriction in patients with chronic cardiovascular disease is an important contribution to the management of this condition. Recent investigation has confirmed the previous clinical observations that patients with impairment of heart function are unable to excrete sodium normally.<sup>8,9</sup> The use of low sodium diets in the treatment of congestive failure is mandatory. Of equal importance is the anticipation of congestive failure by the physician and the institution of measures which will delay this catastrophe. Since in most instances a complete cure of the underlying lesion cannot be accomplished the management of congestive failure attempts amelioration of the symptoms in an effort to prolong the patient's life of comfort and usefulness.

The restriction of sodium in the diet may be conveniently considered at three levels. On an unrestricted diet the average person will eat 3 to 5 gm of sodium daily. This intake can be easily reduced to 1.5 to 3 gm of sodium daily by two simple procedures: the elimination of added salt at the table and the avoidance of highly salted and salt preserved foods, e.g., ham, bacon, salted fish, anchovies, delicatessen meats, olives, salted nuts, potato chips, meat sauces and similar foods. The second level of restriction involves the elimination of all

\* Mead Johnson and Company

† The Upjohn Company

salt in cooking and will reduce sodium intake to 0.5 to 1.5 gm. The third level of restriction involves a careful selection of foods which avoids sodium rich materials, the use of unsalted bread and butter and restriction of many foods to which sodium is added during preparation (e.g., baked products containing baking powder). This restriction should reduce the sodium intake to less than 0.5 gm. per day.

In practice it will be found useful to place patients with the earliest cardiac symptoms of failure on the first level of restriction—that is, approximately 1.5 to 3 gm. of sodium per day. Often, their symptoms will disappear within a few weeks. At a later date when symptoms reappear the sodium may be decreased to the second level of less than 1.5 gm. per day. Eventually it may be desirable to maintain the patient on the lowest sodium level that is feasible. The patient and his family should be given food lists and if available should be seen at intervals by a trained dietitian for assistance with arrangements of menus and advice regarding the preparation of the food. In this fashion the appearance of distressing symptoms and development of congestive failure can often be delayed many months. The ominous prognosis of patients with a history of congestive failure would suggest that by such a delay their lives will have been prolonged. There is no evidence that stringent restriction of salt intake will lead to hypochloremia or other serious consequences. The following case history illustrates the salutary effect of sodium restriction.

H. Q., 50 year old white laborer, was seen in March 1947 with a complaint of nocturia of three weeks' duration. The patient had enjoyed exceptionally good health all of his life. He had always done semiskilled labor. His weight had been maintained within 5 pounds of 132 pounds for twenty years. During the preceding six months he had noted slight exertional dyspnea. For the past three weeks he had experienced nocturia, at first once each night, when seen, two or three times each night. There had been no cough or swelling of the ankles. There was no history of rheumatic fever.

Physical examination revealed a small, tense man in no distress. The precordium was hyperactive with the point of maximal impulse at the left anterior axillary line. There was a grade 2 aortic, systolic murmur and a grade 1 apical systolic murmur. The blood pressure was 200/120. There were scattered, fine rales at each lung base posteriorly. The liver edge was palpable at the costal margin. The urine examination showed a trace of protein in a morning specimen with a specific gravity of 1.014. A roentgenogram showed marked left sided enlargement. The electrocardiogram showed left axis deviation.

The patient was advised to avoid salted foods and to omit all cooking and table salt. He continued his usual activity. No other therapy was given. One month later the nocturia had disappeared and the blood pressure was

165/110 Three months later the blood pressure was 168/90 and six months later 150/95 A year later the blood pressure is 170/90 and the patient has nocturia approximately once per week. The lung bases are clear the liver not palpable. The heart size is diminished by x ray examination The electrocardiogram and heart sounds are essentially unchanged The urine is free of protein

### CONCLUSION

Good nutrition in protracted disease often makes the difference between recovery or death Good nutrition in protracted disease is difficult to achieve because of anorexia and the present inadequacies of parenteral nutrition Much can be accomplished through catering to individual tastes, the use of supplementary feedings nutritional concentrates and tube feedings All of these require good and sufficient dietary help which unfortunately few hospitals are in the position to provide The adequacy of nutritional therapy whether the patient is treated in the hospital or in the home will be determined by the interest and supervision which the physician gives Parenteral feeding is limited by an inability to provide sufficient calories and adequate electrolytes if it is needed over any length of time

Good nutrition in protracted disease occasionally involves restriction of certain nutrients as well as supplementation The encouraging clinical results of sodium restriction in the treatment of impending cardiac decompensation emphasize the contribution of nutritional management to the customary therapeutic plan

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# INVESTIGATION AND TREATMENT OF INFERTILITY

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HERE briefly are listed and discussed the commonest known causes of fertility failure and suggestions are made on how to use easily available methods of identifying and relieving them. Normal health of both mates is assumed. The impediments are grouped under those parts of the female reproductive tract where they effect disturbance as shown in Figure 151.

## CAUSES OF INFERTILITY

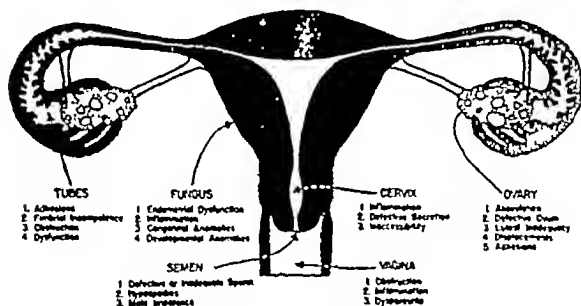


Fig 151.—Causes of Infertility

## VAGINA

### DIAGNOSTIC TESTS

**Obstruction—Technic**—If the history does not tell of failure of intromission (about 25 per cent of affected mates are either ignorant or secretive about this) digital and visual examination may show it to be impossible for the normal erect phallus which is about 1 cm. in diameter. The use of a lubricated glass vaginal plug of this size is useful. Sexual excitement may be expected to relax the introitus a

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little, but if a proper glass form cannot be inserted without much pain, coitus may be adjudged incomplete. Psychogenic resistance as well as male ineptitude or overkindliness must be kept in mind. Vaginal septa must also be sought for.

**Significance**—Although pregnancy may occur when good semen is placed at the introitus, one must suppose in the presence of infertility, that the necessary strand of perfect mucus does not extend from the cervix through the normal vagina, for only in that lane could sperm progress. When access to the cervix is prevented by an inadequate introitus, failure of insemination is very likely.

**Inflammation—Technic**—When, in cases of no intromission, the vagina is not merely psychogenically hypersensitive or anatomically deranged, inspection of the wall may reveal hyperemia, and a smear of the vaginal contents pus or trichomonas, or both. *Monilia albicans* may be demonstrated by culture of the contents in Sabaraud's medium.

**Significance**—Vaginitis is but rarely a long-term cause of coital failure, and likewise it does not often prevent cervical insemination if intromission can be achieved. Seminal fluid protects the sperm until they migrate into cervical mucus.

**Dyspareunia—Technic**—Attention to the patient's story supplemented by digital and instrumental investigation of the vagina manifests this condition.

**Significance**—It may be due to obstruction or inflammation or be purely psychogenic, the cause becoming apparent by careful history and examination.

## TREATMENT

If *anatomic obstruction* cannot be overcome by dilatation with glass vaginal forms of gradually increasing size inserted two or three times daily by the patient herself, or if instruction of the too considerate or inefficient husband is futile, recourse must be had to careful plastic surgery.

*Bacterial vaginitis* can be relieved by semidiurnal 2 quart douches with 0.5 per cent boric acid or sodium perborate solution, or by suppositories (Winthrop) containing 200,000 units of penicillin inserted twice daily for about one week. The *trichomonas* is susceptible to Devegan tablets (Winthrop) inserted morning and night following a douche of 0.5 per cent sodium perborate solution. Floraquin tablets (Searle) may also be effective. The treatment should be continued throughout one menstrual cycle and for the first ten days of each three following cycles even in the absence of symptoms. If the infection persists after such treatment, careful search for the parasite should be made.

in the husband's prostatic fluid, semen and urinary sediment. For *fungus infection* the vagina should first be painted on alternate days for one week with a preparation consisting of gentian violet 1 gm., alcohol 2 cc., and water up to 20 cc. If this fails, suppositories of Propion-gel (Wyeth) may be hopefully inserted daily for one to two weeks.

*Psychogenic dyspareunia* is usually but not always a real problem for the avowed psychiatrist.

### SEMEN, INSEMINATION

The ejaculate must contain an adequate number of normal sperm from the seminiferous tubules in a normal substrate from the prostate and vesicles and must be placed at the right time in the menstrual cycle in contact with favorable mucus extending from the cervical canal. Defective sperm result from dysfunction of germinal epithelium or from intrinsic chromosomal deficiencies. Increased intrascrotal temperature decreases spermatogenesis. Such a temperature change may be occasioned by clothing, woolen suspensories, jock straps and the like. It has been suggested but not proved that varicosities too may increase temperature. Insufficiency of sperm may also be due to dyspermatogenesis and possibly also to inflammation or structural defect in the ducts or accessory secretory glands. Semen produced too soon after a previous ejaculation may also be deficient in number and quality of sperm.

The number, morphology, staining qualities and to a slight extent the behavior of spermatozoa may be observed and appraised by appropriate methods.<sup>1</sup> So little is known of the essential biochemical and biophysical properties of the seminal fluid, however, that study of this medium has not yet entered the clinical field. Even the work on hyaluronidase and on the metabolic functions of spermatozoa and their demands on and utilization of their substrate is still in the research stage.

The most direct and simplest test of the husband's functioning is by postcoital examination of his wife. Normal endocervical mucus varies during the menstrual cycle. Just before and just after ovulation (rarely at other times) it is plentiful, of low viscosity and contains almost no cellular elements. Between menstruation and the ovulation phase and again when this has passed, the mucus is relatively viscous, less plentiful, even scant and is laden with variable numbers of epithelial and white cells and the granular debris of cytolysis.

**Insemination—Postcoital Examination—Technic**—After coitus as near ovulation time as can be determined (see ovulation below), the exposed cervix is wiped clean with cotton, a drop of endocervical

content is removed by long-handled forceps, placed on a flat glass slide, covered with a coverslip, and promptly examined at a magnification of about 200

*Significance*—Favorable cervical mucus about sixteen hours after coitus (intercourse during the night before office examination in the afternoon) should contain 50 or more highly motile sperm per high power field. This means that the male has delivered an adequate number of viable sperm in the right place. Even as few as 10 barely progressive or merely active sperm in most high power fields of optimal mucus may indicate effective insemination. A negative test at times other than the fertile phase is not conclusive. On the other hand, when masses of inert or barely motile sperm are found in viscous cellular mucus characteristic of the infertile periods in the cycle, it is probable that the male is normal within the frame of our present knowledge.

If less than 10 normal progressive sperm are found per high power field the test must be repeated, preferably nearer the time of coitus and closer to optimal ovulation time. Three such negative tests during the fertile phase indicate abnormal endocervical secretions that prevent penetration by normal sperm, or abnormal sperm, ineffective placement of the ejaculate, or a combination of these. Differential interpretation demands, first, examination of semen. This is also indicated if more than 30 per cent of even large numbers of sperm per high power field are seen to be morphologically defective.

*Semen*—EXAMINATION OF ISOLATED EJACULATE (Vaginal contents after coitus have no value for accurate diagnosis)—*Technic*—The ejaculate, after that period of continence usual for the mating under examination, should be collected in a clean glass receptacle. This should be kept tightly covered at room temperature and the contents examined soon after an initial delay of about thirty minutes that permits liquefaction of the substrate and activation and dispersal of the sperm. If more than six hours must elapse before the examination, it may be refrigerated at the expense of motility so that sperm morphology will not be affected.

The volume, opacity and viscosity of the specimen are first noted.

A hanging drop preparation is examined, and the incidence and degree of motility are estimated, as well as the tendency of the sperm to line up in a "phalanx" at the edge of the drop.

The sperm concentration per cubic centimeter is computed as in a white blood count except that tap water is used as a diluent. Finally, a drop is smeared thinly across a glass slide, allowed to dry, then stained for examination of morphology.

**Significance**—The normal values given below may be reduced if the interval since previous ejaculation is less than two days. The semen is normally opalescent, translucent but not transparent widely variable in viscosity and not less than approximately 2 cc. in amount. In the fresh product 80 per cent of the sperm should be progressively motile and there should be 70 to 100 million of them per cubic centimeter. In the stained smear at least 60 per cent of the sperm should appear morphologically normal. The presence of an abundance of white blood cells indicates chronic prostatitis seminal vesiculitis or urethritis but does not necessarily indicate inadequate sperm. However many cells or increased viscosity may impede the migration of normal sperm from their own substrate to that of the endocervical canal. A sperm count of 20 to 40 million per cc. is generally associated with many nonmotile and pathologic forms. This indicates impaired spermatogenesis and lowered fecundity.

When study of the hanging drop or count of sperm reveals semen that does not meet the above standards another ejaculate should be obtained after a longer interval of continence than that common in the coital habit of the males. The optimal time varies with the age of the male and several other factors but is roughly from two to ten days. If two such ejaculates indicate inadequate spermatogenesis detailed examination of the male is indicated.

**Examination of the Male**\*—**Genitalia**—**Penis**—This may be well developed or give evidence of hypogenitalism. Hypogenitalism usually is associated with pituitary disorders. Minor degrees of hypospadias are unimportant but the urethra may open in the perineum and prevent normal placement of semen.

**Testes**—Both testes should be located within the scrotum. Absent or partially descended testes have imperfect spermatogenesis. The normal testes are 4 to 5 cm. in greatest diameter. They are firm and slightly elastic. Small testes or those with soft consistency often have impaired spermatogenesis. The testes may be atrophied to small nutbuns which contain normal interstitial cells but imperfect tubules. Hard areas within the substance of the testis or symmetrical firm enlargements may represent malignant change and imperfect function. Soft fluctuant swellings which transmit light are either hydroceles or spermatoceles and are unimportant in fertility.

**TESTICULAR BIOPSY**—**Technic**.—Local anesthesia is employed. The testis is exposed through a 1 cm. incision in the scrotum. The tunica albuginea is exposed and nicked. Extruding testicular tubules are

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\* This section is contributed by Dr. Fletcher H. Colby, Associate in Genitourinary Surgery, Harvard Medical School.

snipped off with sharp scissors and put in preservative. The nick in the tunica albuginea is closed with one silk or cotton stitch and the skin is closed. The specimen is examined by a pathologist familiar with normal and abnormal spermatogenesis.

**Significance**—Absent spermatogenesis with atrophied tubules makes therapy hopeless. Defective spermatogenesis may be temporary or permanent. If severe the condition is probably irremediable. The clinician should be guided by the pathologist's report.

**Epididymes**—The normal epididymis is felt as a soft structure closely applied to the posterolateral surface of the testis. Rarely the epididymis is absent. It may be widely separated from the testis and this abnormality may have significance. It probably is one of defective development and may be associated with low fertility. Wide separation of testis and epididymis often occurs in torsion of the spermatic cord. Neoplasms of the epididymis are rare and likely to be exceedingly malignant. Most areas of thickening of the epididymes are due to chronic inflammation.

**Vasa Deferentia**—The vas deferens is a hard, smooth, cordlike structure easily identified from other structures within the spermatic cord. Normally it rolls beneath the fingers and can be followed from the lower pole of the epididymis to the base of the scrotum. Occasionally the vas deferens ends abruptly just above the upper pole of the testis. Rarely it may be absent. Occasionally it is represented by a tiny fibrous cord without a lumen. Although spermatogenesis is normal, azoospermia results from such abnormalities of development. Thickening of the vas deferens suggests old inflammatory change. If the thickening is beaded in character, tuberculosis is probable.

**SIGNIFICANCE**—Gross anatomic abnormalities of the vas deferens are often congenital and permanent. Inflammatory changes if not severe may be treated successfully.

**Prostate and Seminal Vesicles**—The normal prostate on rectal examination is a firm, movable gland of uniform consistency. Its apex lies against the triangular ligament and its base blends with the bladder. Between the two lateral lobes a distinct furrow is felt. Areas of increased consistency in the gland in patients below fifty usually are due to chronic inflammatory change. The infected prostate may have a soft boggy consistency but often the gland feels normal even in the presence of severe infection.

The seminal vesicles lie above the prostate closely applied against the posterior wall of the bladder and extend laterally toward the pelvic wall. Normal seminal vesicles usually cannot be felt. When distended with secretion they are briefly appreciated as soft swellings.

above the prostate. Seminal vesicles which are easily felt as firm cord like structures are thickened by chronic inflammation.

Secretion expressed from the prostate and seminal vesicles normally is thin, viscid and milky. Normal secretion contains lecithin bodies, corpora amylacea and none or few leukocytes. The presence of over 10 leukocytes per high power field generally is considered evidence of infection. Secretion from the vesicles often is mucoid. When the mucus is mixed with pus, infection is present. Bloody or rusty ejaculations mean chronic seminal vesiculitis. Abnormal cellular elements and crystalline bodies in the secretion are evidence of infection.

**SIGNIFICANCE.**—The importance of infection of the prostate and seminal vesicles in relation to male fertility is difficult to determine. Many individuals with evidence of severe infection have no impairment of fertility. In others the elimination of minor degrees of infection has appeared to improve fertility. Regardless of the fertility problem, infection is a disease which requires treatment.

**UROLOGICAL EXAMINATION.**—Spermatozoa must travel from the testis through the external urinary canal. Obstruction to the free passage of semen may occur anywhere along this devious course. The actual point of obstruction may be difficult to discover but adequate examination sometimes reveals the cause. Obstruction probably occurs most frequently within the lumen of the vas deferens near the testis or at the termination of the ejaculatory ducts in the prostatic urethra.

Obstructions near the testis are due to inflammatory occlusion of the lumen of the vas deferens or to faulty development. These lesions are demonstrated best by operative exposure of the testes and cords and careful dissection. If normal spermatogenesis is demonstrated by testicular biopsy and there is no obstruction proximal to the epididymis, anastomosis of the vas deferens and epididymis is reasonable.

**EPIDIDYMOVASOSTOMY.**—Azoospermia with normal spermatogenesis demonstrated by testicular biopsy represents the indication.

**Technic.**—Testis and epididymis are exposed through incision in lateral scrotal wall. The vas deferens is isolated from the cord. The vas is examined for inflammatory thickening or areas of constriction. The normal vas is opened near the epididymis by a small longitudinal incision exposing the lumen. A blunt needle is inserted in the proximal lumen and salt solution is injected. If the solution flows easily, no obstruction is present. Colored solutions may be employed and recovered from the bladder by catheter to prove the patency of these ducts. The epididymis is opened at the upper pole and anastomosed with the opened vas deferens using arterial sutures. Bilateral operation is desirable. Wounds are closed without drainage.

*Results*—These are difficult to assess but operation is the only hope in cases of azoospermia. With proper indications and modern surgical technic this operation provides hope for otherwise hopeless sterility problems.

OBSTRUCTIONS WITHIN THE PROSTATIC URETHRA in azoospermia sometimes are visible by examination with the panendoscope. Cysts, tumors or enlargements of the verumontanum are easily seen and treated. Chronic inflammatory changes of the prostatic urethra and vesical outlet may narrow or occlude the ejaculatory ducts. The patency of the ejaculatory ducts can be tested by catheterization and the vesicles visualized by seminal vesiculograms.

*Significance*—Benign lesions, cysts, or papillomas are easily cured and fertility may be restored. Inflammatory lesions may be improved by appropriate therapy including the elimination of infection by antibiotics and dilatation of the ejaculatory ducts.\*

#### TREATMENT

A period of continence of about ten days before ovulation time may be helpful. For *dysfunction of germinal tissue* dietary and hygienic measures are indicated. Attention should be given to clothing and to extensive varicosities. Adjunctive vitamins are to be considered. A few students believe tobacco to be harmful to some men. Prolonged continence is probably of no avail. It is barely possible that androgens, such as methyl testosterone in doses of about 20 mg. ingested or taken sublingually daily, or of similar amounts of testosterone propionate given intramuscularly three times a week may be of some benefit after six months of treatment. Larger doses may suppress spermatogenesis. The value of the pituitary and chorionic gonadotropins is still only conjectural. They may be tried for six months. Those suggested are the pituitary extracts such as Gonadophysin (Searle) given intramuscularly in doses of 100 to 500 units three times weekly, or the serum gonadotropins such as Gonadin (Cutter) and Gonadogen (Upjohn) in doses of 100 units intramuscularly three times weekly. Chorion hormone such as Korotin (Winthrop) in doses of 500 units three times weekly also may be given intramuscularly.

For *inflammation of the prostate or vesicles*, massage and the antibiotics may help. For *vasal or epididymal obstruction* competent surgery is the only recourse and can be expected to be of value in about 10 per cent of the cases. For *penile deformity*, surgery is to be considered, but if coitus is satisfactory, not until after artificial placement of the ejaculate at the external os at ovulation time during at least

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\* Here ends Dr. Colby's gratefully acknowledged contribution.

six cycles has failed (It should be mentioned that artificial insemination with the husband's normal ejaculate in cases of full intromission is not helpful) When *impotence* prevents ejaculation in the vagina psychotherapy is usually in order. Only rarely is the semen adequate for fertilization when failure of erection is due solely to hormone deficiency. In these rare cases exogenous androgens may suffice. Intramuscular injections of 25 mg of testosterone propionate daily for one month and then thrice to twice weekly enteral or sublingual daily doses of at least 20 mgm of methyl testosterone or the implantation once every three months of 2 to 3 testosterone pellets (Schering) each containing 75 mg can be expected to reestablish potency in the absence of psychogenic fault.

### CERVIX UTERI

#### DIAGNOSTIC TESTS

**Inflammation**—*Technic*—This is the same as for the postcoital examination.

**Significance**—When cervical mucus at ovulation time contains pus there is endocervicitis and possibly endometritis. Of minor degree this may not be significant but must not be underestimated. The presence of many leukocytes at times other than that of ovulation may be physiologic.

**Secretion (insufficient or excessive)**—*Technic*—See postcoital examination.

**Significance**—Mucus may be too scant or too profuse at ovulation time. The former is rare. When a pinpoint os prevents entrance of standard smooth forceps the flow of secretion may offer too small an area of contact with semen for enough sperm to escape from it before lethal vaginal secretions destroy them. If the os is found wide open and great gobs of clear mucus bathe the whole portio the expense available to sperm may permit wasteful wandering of too many of them that otherwise would perforce enter the canal.

**Inaccessibility**—*Technic*—The distance between symphysis and cervix is estimated in centimeters by digital examination. Repeated postcoital examination may be confirmatory.

**Significance**—When the cervix lies less than 4 cm from the posterior border of the symphysis and insemination is imperfect maladaptation of penis to cervix may be present.

#### TREATMENT

For *endocervicitis* superficial cauterization and topical medication are valueless. The sulfa compounds and penicillin given at least dur



ing the first ten days of several successive cycles in doses adequate for other infections may be of great value. If the cervicitis is marked, careful and conservative conization of the external one half of the cervical canal, supplemented by treatment with antibiotics, is in order. Removal of too much endocervical tissue results in a cervix comparatively dry, and sperm cannot jump. Similarly, if the glands produce a great excess of even normal mucus this may be diminished by proper conization.

To evoke *increased secretion* is difficult. Estrogen may help, but if given in daily doses exceeding 0.25 mg of diethylstilbestrol, or 0.025 mg of ethinyl estradiol, suppression of ovulation may result. It is conceivable that the old-fashioned operation of posterior discission of the portio might help in this condition, if repeated dilation of the external os following several menstrual cycles fails.

*Inaccessibility*—When the cervix lies just superior to the symphysis and is by-passed by the phallus, anterior orthoposition of the fundus with resultant backward placement of the cervix may be possible. If this cannot be accomplished manually and maintained by a pessary, competent surgical intervention should be reluctantly considered and indulged in only after all other factors of fertility are eliminated as possible causes and modification of coital technic proves unavailing. Intromission of only the glans with intracervical coitus may be accomplished if, after insertion of the penis, the husband's thighs are placed lateral to the wife's. This, with delay of withdrawal, should first be given repeated trials during successive ovulation phases and checked by postcoital examination.

## UTERINE FUNDUS

### DIAGNOSTIC TESTS

**Endometrial Dysfunction—Technic**—If catamenia occurs at fairly constant intervals, and especially if infrequent, recurrent flow is similar in duration, quality and amount, it is very likely that full progestational changes in the endometrium are produced during most cycles. Study of basal temperature charts (see below) may be used to supplement such consideration. Cytologic morphology and staining qualities can be interpreted by those competent, in the material obtained during the last week of the cycle by biopsy (Fig. 152),\* or by curettage.<sup>2</sup> The very slight danger of abortion if biopsy is performed after the seventh postovulatory day and before the first day of menstruation must be kept in mind. (Timing of ovulation is discussed below.)

\* I am indebted to Dr. Somers H. Surgis, now of the Massachusetts General Hospital, Boston, for all photographs.

Biopsy specimens are easily obtained in the unanesthetized patient by dexterous insertion of a special curet of small caliber. While negative pressure is established in the cannula by the attached syringe the fundal portion high up on the anterior or posterior wall is rapidly stroked. The tissue should be promptly fixed in Bouin's solution.

*Significance*—When, in the sections stained with hematoxylin and eosin glandular and stromal cells are seen to be characteristic of any day in the postovulatory cycle and subsequent flow occurs after an interval which added to that postovulatory diagnostic day approximates fourteen days, one may fairly assume that the corpus luteum has functioned normally at least during the cycle of the test. Similarly

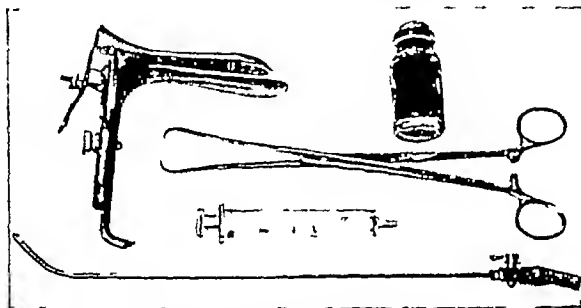


Fig. 152—Equipment for endometrial biopsy: speculum, bottle of Bouin's solution, tenaculum, syringe to apply suction, suction curet. Obtainable through Thomas W. Reed Company, Boston, Mass.

of menstrual periods strongly suggests similar luteal functions during other cycles. If the interval between the postovulatory diagnostic day and the day of flow is less than twelve on repeated biopsies or the tissue is morphologically atypical, one may suspect incomplete luteal function. (Once the tissue has passed the proliferative phase almost never will the sum surpass fourteen, and in those rare cases, not more than sixteen.)

The stained tissue can tell us only whether or not and approximately how long, and how well the corpus luteum functions. We can but assume that normal activity of this gland signifies normal ovulation. Nor does the specimen by usual laboratory treatment attest normal histochemical function of secretory endometrium. Study of this is yet an urgent research problem.

If the endometrium is found to be still in the proliferative phase, and flow occurs within ten days, a failure of ovulation may be assumed in that cycle. Study of temperature charts with perhaps repeated biopsy is indicated.

**Inflammation—*Technic***—Postcoital examination of cervical mucus together with biopsy or curettage of the endometrium are of use here.

**Significance**—If pus is found in ovulation mucus, nonspecific endometritis may be present, though usually endocervicitis is the source of the leukocytes. White cells in the endometrium are physiologic, but a generalized leukocytic infiltration of significance can easily be recognized by the well trained pathologist. One must be constantly on watch for the characteristic lesions of tuberculosis. Hereabouts this is found in about 0.6 per cent of cases.

**Congenital and Developmental Abnormalities—*Technic***—Bimanual palpation, transcervical exploration by means of the uterine sound, and uterography are at our disposal. In doubtful cases it is well to use all three methods.

**Significance**—To bimanual palpation the fundus feels much smaller than it is actually. If it feels less than 3 cm. wide it is probably hypoplastic to a significant degree, regardless of menstrual performance. In such cases of true underdevelopment the isthmus, that part between the enlarged upper portion and the portio, is usually found to be disproportionally long, as of the order of 2 to 3 cm. Why such juvenilism is an impediment is not clear, for good eggs, properly fertilized, often safely find their way into maternal blood sinuses wherever they happen to embed. Can it be that in these hypoplastic uteri transport of the blastula through the uterine portion of the tube is imperfect, or that such degrees of hypoplasia are associated with defective tubes as well? Nor are we sure that myometrial activity has nothing to do with migration of sperm, however unlikely this may be.

The bicornate as well as the didelphic uterus is more certainly identified by sound and uterogram. As in the hypoplastic variety pregnancies sometimes occur and may be normal, but miscarriages and monstrosities are more numerous than they are when the fundus is normal. It is conceivable that the vascular equipment of these deformed uteri is unable to reach adequate degrees of expansion. Attention should again be directed to our ignorance of whether or not myometrial activity contributes to the prompt delivery of sperm to the tubes. It has been shown in guinea pigs that aged sperm may inaugurate unproductive growth of ova.

Retrosflexion of the fundus, too may be discovered by palpation and sounding. It may be a factor of infertility if it causes passive congestion or by traction on the tubes and tubo-ovarian ligaments (which is not exerted in most cases) causes interference with normal tubo-ovarian function.

Fibroids are commonly encountered. Though very often they do not impede fertilization they may hinder by their size or position the movement of sperm or blastula or may prevent normal nidation and adequate placental development.

### TREATMENT

*Secretory dysfunction* is probably due to defective luteal activity yet with our limited knowledge of the functional endometrium it is usually a doubtful diagnosis at best. If it is suspected repeated biopsies should be competently studied. When this diagnosis is warranted recourse may be had at present to progesterone in doses of at least 10 mg. on alternate days during the postovulatory phase of the cycle of exposure and continuing until pregnancy is diagnosed. The chorion hormones (such as Korotrin Winthrop) may be used also with or without progesterone during the same period in doses of the order of 5000 units on alternate days. This stimulates the corpus luteum. Eventually the pituitary gonadotropins may become helpful.

For *endometritis* other than that which is tuberculous antibiotics often without curettage should be tried throughout several consecutive cycles. Tuberculosis formerly indicated hysterectomy and bilateral salpingectomy. Streptomycin may make such radical treatment unnecessary.

Constitutional *hypoplasia of the uterus* reflects a disorder of puberty and early adolescence and is exceedingly resistant to available therapy. Treatment is still highly experimental. Theoretically effective doses of estrogens usually will inhibit ovulation. They may be tried for a few months in doses such as  $2 \times 0.05$  mg. of ethinyl-estradiol (Estinyl Schering) or 5 mg. of diethylstilbesterol with the justifiable expectation that ovulation if stopped will be resumed with cessation of treatment. If tolerated the chorion hormone (Korotrin Winthrop) may be injected in doses of 1500 units, two to three times weekly while treatment with estrogen is pursued. The experimental nature of this therapy must be kept in mind and menstrual disorders expected.

*Anatomic deformities* whether developmental or acquired are to be viewed only with suspicion while all other factors of fertility are explored. Especially when the uterus is partially or completely dupli-

cated, and when fibroids are not more than 5 cm in diameter, and when retroversion is not associated with passive congestion or with prolapsed ovaries, one may hesitantly consider and not eagerly resort to surgery

### FALLOPIAN TUBES

Ignorance doubtless clouds our insight into the complete function of the fallopian tube. Perhaps its fluid normally offers more to the ovum and sperm than a protective medium. The biochemicals in solutions may be of value to both gametes and to their conjugated zygote. We know not the nature of these substances or of the method of their utilization. At the moment the most we expect of the tube is that it will collect the ovum and transport it to the uterus, providing a fluid medium in an unobstructed channel through which, also, sperm may travel. For these purposes there must be patency and a lining that secretes fluid and, by means of cilia (aided doubtless by myosalpingial peristalsis), conveys this, with some peritoneal or follicular fluid, into the uterus. This current too, must be sufficiently forceful and so powerfully applied that it will literally suck the ovum into the tubal ostium preferably from the surface of the ovary and, failing that, then from the peritoneal fluid into which the egg had escaped. Normally, muscle fibers in the tubo-ovarian ligament, the mesosalpinx and well developed fimbria bring about the application of this fan shaped flaring end of the tube to the ovary so as to form a virtual ovisac. Malformation of the fimbria, adhesions among them, or between them and adjacent structures, may effectively interfere with this mechanism.

### DIAGNOSTIC TESTS

**Tubal Competency —INSUFFLATION —*Technic*** —By means of such a cannula as is depicted in Figure 153 \* and a source of carbon dioxide as shown in Figure 154, gas may be injected into the fundus under controlled pressure. This should never exceed 200 mm of mercury, usually nothing is gained by using a pressure higher than 180 mm. The examination is best performed two or three days after all menstrual flow has ceased or early in the last week before menstruation. Of course it must never be made when there is a possibility that the vascular system of the endometrium is disrupted. The presence of adnexal inflammation also contraindicates the test. During and immediately after ovulation synchronous bilateral tubal contractions may give a falsely negative result. The rubber acorn is fixed at a distance from the end of the cannula such as will permit the terminal

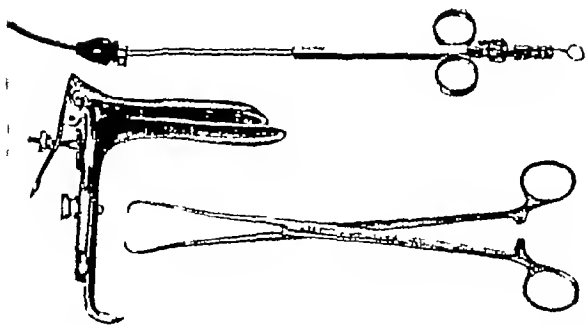


Fig. 153.—Instruments for insufflation: speculum, Jarcho cannula with rubber acorn, tenaculum (that is frequently not necessary).

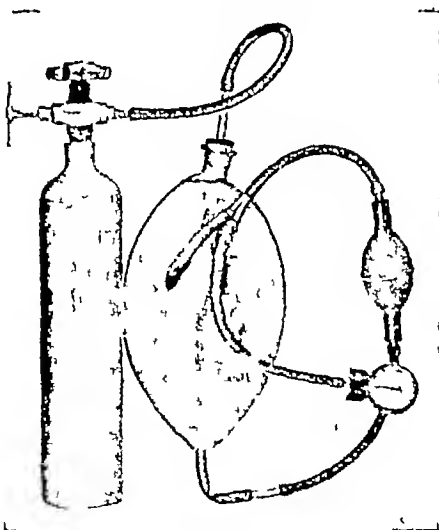


Fig. 151.—Equipment for supply of coal in distal tank with valve, tubing and bag to reduce pressure, bulb to control pressure, manometer to register pressure.

openings in this tube to pass the internal os while the tip of the acorn is fitted into the external os. The cannula is attached to the rubber tube and flushed out with gas, and then, gently, the end is passed through the cervical canal. Occasionally it is necessary to grasp the cervix with the tenaculum either to facilitate placement of the cannula or to press the acorn tightly into the external os to prevent leakage of gas. While the pressure is raised very slowly, the manometer is closely watched, and pressure need not be elevated above the point at which gas escapes from the uterus. If the gas fails to pass at 180 mm, the pressure should be released and the process repeated two or three times. Pressure should never be applied violently. When during one cycle gas fails to pass, the test should be repeated during one or two subsequent cycles. It is rarely necessary to use more than two bulbful of gas. If one tube is patent the carbon dioxide escapes into the pelvis and from there, when the patient sits up, it rises to the diaphragm where irritation causes, in one or the other shoulder, a mild discomfort for perhaps ten minutes. In the absence of pelvic adhesions this occurs promptly. Air is undesirable as a test substance, for the slowness of its absorption may cause a prolonged sense of substernal pressure or pain in the shoulders.

*Significance*—When gas escapes from the uterus without increased pelvic pain it means merely that at least one tube is patent. The other one may be. Pain in the shoulder is confirmatory but not an essential proof. If gas apparently escapes at a pressure above 140 mm of mercury but there is pain in the pelvis, resistance in peritubal adhesions or even dilatation of a "clubbed" tube must be suspected. When the manometer needle remains at any point during sustained but not increased squeezing of the bulb, it must mean that gas is not passing out of either tube. This may indicate that both oviducts are obstructed. They may be merely in synchronous contraction. Repeated negative tests strongly indicate closure. A positive test does not mean that the tubes function normally, but merely that one or the other tube is patent.

*SALPINGOGRAPHY* (Fig. 155) —*Technic*—This is the same as for insufflation, using a syringe containing a roentgen-opaque medium instead of a source of carbon dioxide. At the same elective times in the cycle, not more than 10 cc of a solution of contrast medium such as Diodrast (Winthrop) or Iodochloral (Searle) is gently injected under a pressure, again not exceeding 200 mm of mercury and, as the apparatus is held in place, an x-ray film is obtained. When the liquid cannot be injected with the limited pressure stated and severe pelvic pain is experienced while the plunger of the syringe is pressed, one

should suspect obstruction. Many roentgenologists find helpful several films taken during the injection.

**Significance**—Delineation of the tubes indicates patency of the canal. Spill of the medium into the pelvis shows that one or both tubes are open at both ends. Limitation of the shadow within the uterotubal system usually indicates obstruction. Again one should remember that patency does not necessarily mean integrity of function.

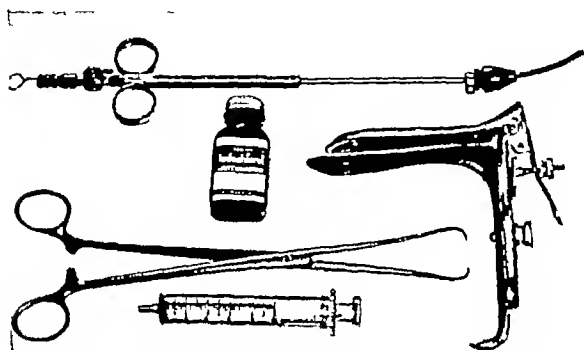


Fig. 155.—Equipment for uterosalpingography: speculum, Jarcho cannula, supply of contrast medium, syringe, tenaculum.

**CULIDOSCOPY** (Fig. 156) —**Technic**—Dr. Albert Decker of New York has helpfully modified the instruments of peritoneoscopy so as to permit easy visualization of part of the uterus and of the tubes and ovaries. With the patient in knee-chest position, the bowel and bladder having been previously emptied, the stilette and sheath are introduced into the cul-de-sac by forcing an opening through the posterior vaginal wall in the midline 4 or 5 cm. posterior to the reflexion of the portio. Maintenance of the knee-chest position with proper thigh and shoulder support as well as the procedure itself may be uncomfortable for the patient. Fifteen minutes before examination 1 cc. of demerol hydrochloride (Stearns) or  $\frac{1}{4}$  grain of morphine may lessen general discomfort. Some use infiltration of the posterior vaginal wall with a 0.5 per cent solution of novocain to dull local sensitivity but this may separate peritoneum from vaginal epithelium and impede puncture of the former by the sheathed plunger. Insensibility is not essential but now I find anesthesia with intravenous pentothal sodium (Abbott)



started after the patient is in position very satisfactory. The special telescope is inserted through the properly placed sheath. As this is a surgical procedure to be used only by qualified persons, details are omitted here. Reference should be made to the discussions of Decker<sup>3</sup> and To Linde<sup>4</sup>.

**Significance**—The technic may reveal impalpable tubal adhesions as well as congenital deformity of the fimbria. (Much information regarding the ovaries may also be obtained. See below.) Care must be exercised not to misinterpret physiologic cyclic changes in the appearance of the tube. Purple enlargement especially during the pre- and

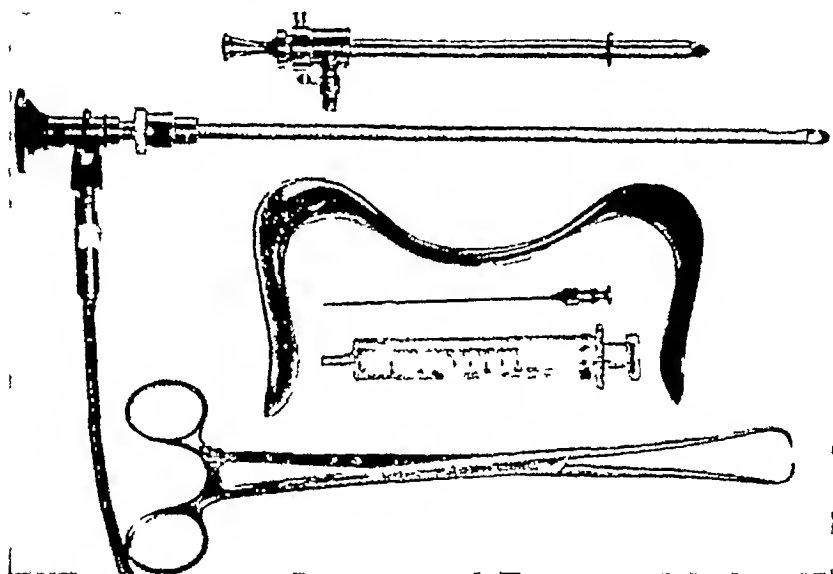


Fig. 156.—Equipment for culdoscopy: speculum, syringe and needle for local anesthesia if desired, cervical tenaculum, sheath with plunger, telescope. (The last three may be obtained from American Cystoscope Makers, Inc., 1211 Lafayette Avenue, New York 59, N. Y.)

postovulatory phases may indicate salpingitis. Bands of adhesions extending from the fimbriated end or the region of the ampulla to the ovary or other organs, or to the pelvic walls, may mean that the tubal "pick-up" mechanism is faulty. The technic is new. More details of significance may become apparent with more extensive experience.

#### TREATMENT

Many clinicians believe that repeated insufflations clear the tubal lumen of postulated filmy adhesions or detritus. Perhaps so. Others have advised repeated flushing of the tubes with the contrast medium.

used for roentgenography. If this were of any use I would think lavage with 5 to 10 cc. of normal salt solution or Ringer Locke's solution would be preferable. Such treatment is of problematrical value and quite experimental. It may not be without danger of inducing inflammatory adhesions. Perhaps a little penicillin should be added to the liquid. If such treatment is indulged in it should be used sufficiently long before ovulation as to permit natural removal of all traumatic blood from the oviducts for such will doubtless inhibit sperm penetration of the ovum. Nor must lavage be done so soon after menstruation as to allow transplantation of viable endometrium to the pelvic peritoneum. Furthermore the procedure is not without danger of peritoneal shock.

*Salpingitis* is best combated by antibiotics.

*Adhesions* with or without tubal closure respond only to surgery and thus of the most delicate kind. Fine nylon sutures are probably the least irritating. Forms to keep open the established lumen at the ovarian end and at the opposite end in cases of resection and implantation are desirable but the ideal kind has not been found. Removable ones of glass, metal or plastic are being tried by various operators. Perhaps absorbable human fibrin film (Cutter) of proper shape and size may prove helpful. Several meticulous surgeons have emphasized the probable value of prompt postoperative antiseptics with sulfa compounds and penicillin. Possibly disinfection of the alimentary canal by ten days preoperative ingestion of about 12 gm. daily in divided doses of sulfathiazidine or sulfasuxidine (both Sharpe and Dolme) would be of value. Of doubtful merit I think is postoperative flushing of the uterus and tubes by gas or liquid. Some competent surgeons disagree with me. The danger of embolism must not be minimized and is prohibitive if curettage has been performed.

## OVARY

### DIAGNOSTIC TESTS

**Ovulation**—Tests for ovulation all pertain to function of the corpus luteum for with the exception of mittelschmerz that is of unknown cause and therefore has no validity it is only when progesterone effect is detectable that we may assume ovulation. Even such assumption may be unwarranted for entrapped ova are not unknown in several other species. For our purpose progesterone has these detectable effects: (a) it increases waking temperatures, (b) it causes characteristic cytologic changes in the proliferated endometrium and (c) it makes the menstrual flow similar in many successive cycles and usually makes periodic the onset of flow.

"WAKING TEMPERATURES" <sup>5 6</sup> *Technic*—So-called "basal body temperatures" or "waking temperatures" may be determined preferably by vagina or rectum as soon as the patient awakes and desirably at about the same time each day. When progesterone becomes effective the level of the temperature is higher than it was before.

*Significance*—When readings are charted against days in the cycle, the low point from which the temperature rises to stay is probably indicative of the approximate time of ovulation. If the completed curve between the onsets of two periods of flow is not diphasic one may assume that no corpus luteum has been formed and therefore that ovulation has failed. The temperature may rise abruptly from the low point or do so gradually day by day. Pregnancies have occurred during cycles in which either graph was recorded.

ENDOMETRIAL BIOPSY—*Technic and Significance*—Both have been discussed.

MENSTRUAL STUDY—*Technic*—The patient is asked specifically if her periods resemble each other and the recorded dates of menstruation are checked.

*Significance*—If, in length, almost all cycles are of the order of  $X$  plus or minus 2 ( $X$  being any number between 26 and 30 inclusive), the woman probably ovulates in most cycles. If menstruation is very infrequent, yet the periods of flow are quite similar (and especially if there is "essential dysmenorrhea"), again, the woman probably ovulates from sixteen to twelve days before the first day of each flow.

Defective Ova—We have no means of knowing how "good" is the released ovum. In lower pluriovulating mammals, the production of imperfect ova is an accepted event. It seems likely that in women in their forties eggs insusceptible to fertilization are very frequent. It is likely that many early abortions are attributable to the same defect, as well as to the possibility that deterioration of an originally normal egg had started before cleavage began. Women who have undergone appreciable radiation may likewise produce faulty ova. From the biologists we learn that it is also probable that the daughters of mothers who have been exposed to perhaps even small doses of radium or x-ray may produce defective gametes or that their ova may carry recessive defects which if complemented by similar spermatogenic faults may result in abnormal zygotes or embryos. One should be mindful of these considerations when all available tests for reproductive functions fail to expose a likely cause of infertility.

Luteal Inadequacy—This is a theoretic hindrance to fertility. We have good reason to believe that the functional endometrium with its vascular equipment regresses if the supply of progesterone fails.

before the trophoblast has begun its production of the same or a similar protective hormone and has become able to deliver this into the maternal blood stream. Is it not possible that imperfect luteinization of the emptied follicle fails to cultivate a serviceable endometrium during the four to six postovulatory days anteceding nidation? The luteal body normally undergoes regressive changes while the blastula evolves into the trophoblast and embryo. Chorion hormone from the newly formed trophoblast entering the maternal circulation reverses luteal regression. Are some corpora lutea critically insensitive to the new stimulation, and so do they fail to secrete the increments of progesterone necessary to protect the endometrium and its vessels until the conceptus has established access to maternal blood?

*Technic*—Endometrial biopsy has been discussed already as has the validity of temperature graphs as gauges of luteal integrity.

*Significance*—As has been mentioned if on repeated examination the endometrium does not reflect in predecidual development of glands, stroma and vessels, effective action of estrogen and progesterone characteristic of the premenstrual day on which the biopsy is made we may suspect luteal dysfunction. Since the increased waking temperatures of the second phase of the normal cycle have been shown to be due to progesterone we may likewise entertain doubt that the corpus luteum is normal. It has been written above that a staircase rise of temperature during the several days following the morning of the low point has been seen in many cases in which pregnancy occurred. Perhaps such success is possible only if the trophoblast is unusually spirited or precocious thus compensating for a truly defective source of progesterone.

*Displacements and Adhesions*—The ovum within its enveloping granulosa is inert. It drifts out of its vesicular sac in a small current of follicular fluid. This latter must make contact with that part of the peritoneal fluid that is subject to the pull of the tubal cilia and peristalsis. If pelvic disease such as critically located endometriosis or if uterine or intraligamentous fibroids or if adhesions displace the ovary from the area of influence of the tubal current the chances of the eggs entering the ostium of the oviduct must be diminished.

*Technic*—Bimanual palpation may reveal adnexal abnormalities. Some have used highly specialized roentgenography with previously established pneumoperitoneum to detect ovarian displacements. Culdoscopy as described above or laparotomy offers a more direct and accurate diagnostic method.

*Significance*—When palpable disease in the vault is encountered or adhesive derangements of effective tubo-ovarian relationships and

mobility are visualized, we may justly assume that most if not all ova are lost in the pelvic fluid

### TREATMENT

Would that we had even one dependable method of inducing the refractory ovary to ripen and discharge oval. Close attention to general health and hygiene, with, for good measure, perhaps a little desiccated thyroid in tolerated doses, may help. Secondary anemia should be relieved. Regulation of menstrual flow for six months is advisable. This is best accomplished by twenty-one days of an oral estrogen such as 0.5 mg of ethinyl estradiol (Ethinyl, Schering) (some prefer diethylstilbesterol in doses of from 2 to 5 mg daily) followed by at least four daily injections of at least 10 mg of progesterone (Proluton, Schering). If 25 mg of progesterone can be afforded, results may be better.<sup>7</sup> Flow can be confidently expected within seven days of the final injection. Estrogen medication should start again on the first day of this induced menstruation. When such cyclic treatment has prevailed for six months, subsequent or even, strangely, intercurrent ovulation may occur.

Active preparations of gonadotropins are available but are sadly ineffective as provocateurs of ovulation. The mare's serum extracts such as Gonadin (Cutter), and sheep's pituitary extracts such as Gonadophysin (Scarle) may be used. The latter will stimulate follicular growth when given intramuscularly in three to five successive doses daily of as little as 100 units, followed on two more successive days by injections of 500 units daily. The contained ova have the appearance of maturity but what we want is their release. Such treatment appears to be effective priming for this event. We need a detonator. Since the chorion hormone preparations are very unreliable as such, experiments are in progress to supply this detonation by use of a luteinizing fraction of sheep's pituitary or by making possible more rapid absorption and so less extensive catabolism of the same follicle stimulant. Intravenous injection of the chorion hormone is forbiddingly dangerous for either it itself or, more likely, its vehicular protein molecule is usually very toxic. The bold and, I suspect, too impetuous therapist may try adjunctive use of the antihistamine preparations. A safer procedure is doubtless soon to be evolved.

When habitual production of defective ova is manifest, suppression of fertility is in order. Insufficiency of progesterone may be feebly compensated for by injections of 10 to 25 mg of progesterone on alternate days, at least, during the postovulatory phase of the cycle of exposure to pregnancy. Dr. Olive Smith has presented some evidence<sup>8</sup> that

diethylstilbesterol in doses not exceeding 0.25 mg daily may stimulate the corpus luteum. The chorion hormone (Korotrin Winthrop) in doses of 5000 to 10 000 units on alternate days after ovulation will surely do this.\*

As is the case with tubal adhesions, disease and deformity or when malposition or limitation of motion of the ovary prevents delivery of the ova to the tube expert, meticulously delicate surgery with thorough adjunctive antiseptics may establish fertility.

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## BRIEF PSYCHOTHERAPY IN MEDICAL PRACTICE

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One of the most remarkable developments in the field of medicine within the last few years has been the rapidly growing recognition of the important part that personality factors play in the causation of physical illness. Based upon centuries of practical experience but stimulated more recently by systematic observations and experimental investigations this aspect of medical practice known as psychosomatic relationships has had a profound influence upon the general profession. It has permeated the literature to a point where there is hardly a journal medical or lay that does not contain some contributions on the subject. It is assuming a place of importance in both undergraduate and postgraduate medical education. It has become a subject of lively interest wherever medical men meet whether it be at scientific conferences or in informal discussion. The rate of this progress is particularly impressive when we consider the fact that these last few years have brought an unusually rich crop of important contributions ranging from penicillin to the possible utilization of atomic energy for medical purposes. And yet the keen interest in psychosomatic disorders and the appreciation of the need for coping with them have continued to grow both in scope and intensity.

Experience teaches us however to keep in mind the fact that great enthusiasm in accepting a new idea does not always carry with it the assurance of lasting effects. Those of us who are convinced of the importance of the contribution that the proper application of the principles of psychosomatic medicine can make are aware of the danger of its running through the usual cycle of a fad—a danger which is, paradoxically enhanced by the very great popularity which the subject now seems to command. Medicine is preeminently practical in nature throughout history we find numerous examples of this type in which one begins to wonder whether the new idea presented any practical value as soon as the first effects of the novelty wore off. In the case of psychosomatic disturbances just as in any other field of medicine practical values are measured in terms of prevention and treatment. Theoretically one may be interested in or even convinced of the likelihood

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of an emotional conflict resulting in a physical symptom. In the long run, however, the interest will be maintained only if we develop clearly expressed and generally available methods whereby such symptoms can be prevented or treated. This need is most clearly demonstrated in the field of medical education, whether it be at the level of refresher courses, resident and intern training or medical college. Most of them accept the underlying principles of psychosomatic relationships quite readily. But granting the fact that physical illness can be wholly or largely caused by emotional problems, personality deviation, or social stress, they invariably counter with the question: How can we as physicians get at these facts and what can we do to help these patients?

The natural answer to such questions, of course, is *psychotherapy*, but the term itself has no meaning unless it can be presented in a systematic, teachable manner with some assurance that eventually and, without the need of highly specialized instruction, the general medical practitioner could make use of such a method in the practical treatment of his patients. Unfortunately one starts out here at a disadvantage. The term psychotherapy has through the ages acquired an atmosphere about it that either frightens or discourages the beginner from venturing into it. On the one hand, the old time concept of this method, starting in with the mumbo jumbo of the medicine man and going through to the similarly unscientific and highly subjective practices of mesmerism and the early stages of hypnosis, has a flavor of mysticism and even charlatanism to it. It does not appeal to the practically minded physician, particularly as he is taught systematically the matter of fact, objective, scientifically based principles of therapy in other fields of medicine. On the other hand, the more recently developed methods, of which perhaps psychoanalysis is the most systematic, have built up such an impressive and complex structure, are so cumbersome and time consuming to administer, and also so difficult to learn that it quite justifiably discourages the student from even considering them.

Thus we are presented with an apparent dilemma. Anyone who goes into the study of medicine today becomes thoroughly imbued with the idea that physical ailments can be and very frequently are produced by personality problems and yet no systematically organized form of therapy which the student can learn, and be in a position to apply practically, seems to be available.

The situation, however, has changed materially within the last few years. The realization of the need of simpler and more objective methods has led to experiments in making psychotherapy more generally available. The various methods that have been developed have each added enough of solid factual material which could be used in building

up a more simplified and more easily applicable procedure. Further more it became quite obvious that in psychotherapy just as in any other field of therapy we must distinguish the highly complex and fortunately also infrequently occurring personality disturbances from those which develop under less complicated conditions and therefore, are more easily accessible. For the treatment of the former which we might call the specifically psychiatric problems complex methods will always be needed and these will have to be practiced by those who have had a specific training in the field. For the more simple types of conditions which fortunately are the ones that we encounter most frequently less complex therapeutic methods are available which can and should be learned by anyone who engages in the practice of medicine.

Actually within the last few years, and particularly in response to the great need that arose during the war years a series of psychotherapeutic techniques have been developed which have the advantages of being more generally applicable and yet require less specialized technical skill. These are at the present time gradually being systematized into what is known as the method of *brief psychotherapy*. In general this method can be expressed in terms of (a) *therapeutic goals* that are set for the procedure and (b) *techniques* of comparatively simple and teachable type that can be used in order to get to these goals. It is true that this procedure is not adequate, nor does it propose to unravel some of the more complex problems in human nature but in the large majority of somatically ill people it can be utilized with satisfactory results. The procedure lends itself to short term treatment because in the first place it deals with the more obvious and therefore more easily accessible stress situations and at the same time the actual method permits a cooperative approach in which the medical man can utilize effectively a number of allied disciplines whose representatives can carry a large share of the burden.

In the following presentation of *brief psychotherapy* I would like to offer a systematic even if somewhat sketchy description of the goals that are set in this procedure and the methods which help us in attaining them. It goes without saying that this will not be an exhaustive treatise on the subject nor is it possible in such a brief scope to illustrate these methods by the aid of case material. For both of these we will refer the reader to some excellent monographs that have recently been written on the subject. Several of these will be listed in the bibliography but I would like to recommend particularly the report on *Teaching Psychotherapeutic Methods* published by the Commonwealth Fund which presents the subject in a practical and clear manner.

## THE GOALS OF PSYCHOTHERAPY

**Understanding of Relationships**—We start out with the fact that emotional conflicts, traumatic personal experiences and social stresses can and do give rise to the development of physical illness, or, where such illness is present, tend to exaggerate or perpetuate it. This, therefore, leads to the logical question as to what is the nature of these causative factors and what is their relationship to the illness with which we are dealing. The answer to this question will provide us with the basic material for the treatment and, therefore, the understanding of relationships becomes our first goal, just as it is the first goal in the practice of any form of therapy. However, there are certain features which are specifically more important in this procedure and should, therefore, be more firmly emphasized. Given a case, say of mucous colitis where a thorough physical check-up has either been done or, what is more likely to be the case, is contemplated, we will want to know what were the social settings, the family situation and the personal attitudes and experiences of the patient at the time when the symptoms first developed. Can any definite relationship be established either in time or in content between problems in this area and the development of the first signs of the illness? Was the patient faced by some special stress situation? Did the physical symptoms, as they developed since then, bear any systematic relationship to the rise and fall in these personal difficulties? Were the physical symptoms in any way useful in by-passing the existing problems or the need of dealing with them? In other words, has the sickness in one way or another, even though it has incapacitated the patient, at the same time furnished the means of evading some important issues?

The next set of data to consider is (a) whether there were any experiences in the patient's life which have made him more vulnerable, more susceptible to the stress situations which he had to face at the time of the onset of the illness, and (b) whether anything has occurred in the life of the patient which has conditioned him to react to such stress situations with the particular type of symptom or symptoms that he now shows. Have patterns been established in the family and wider circle of the patient's environment for reaction of this type? Were there, for instance, any frequent occurrences of gastrointestinal disturbances in the family setup affecting persons who were of particular importance to the patient and under conditions which are meaningful in relationship to the problems under which the patient is laboring now? Finally, the nature of the whole family setup and early conditions under which the patient grew up must be understood for the purpose of finding

whether constitutional predispositions could be discovered that bear a definite relationship to the presenting symptom complex.

It is important to appreciate that in treatment of this type the very search for relationships in itself forms part of the treatment. In the first place, as the patient begins to understand the reasons for the development of the symptoms he is on the one hand unable to utilize these symptoms for that purpose and on the other he begins to find more acceptable forms of solution for these problems. It is because of this that the primary aim in this process is that the patient should get a clear understanding of these relationships whether the physician does or not. Secondly as this process of discussing the life history of the patient progresses the patient cannot help but develop a deep emotional attachment to the therapist. The therapist becomes a friend a sympathetic listener a person interested in the life and experiences of the patient.

**Physician Patient Relationship**—This then introduces the second goal towards which we are aiming namely the establishment of an adequate physician patient relationship and the assurance of emotional participation by the patient during the treatment. Very often we find that some of these problems are so near the surface that following a brief interview with the patient the physician may be able to recognize the relationships fairly clearly and it would be a simple matter then to enlighten the patient on the meaning of his symptoms. Experience teaches us however, that unless the patient brings up these experiences himself and gains an emotional insight by actually reliving them the results are either not obtained at all or are purely on a verbal level without any lasting effect on the patient's condition. The therapist must from the very beginning impress the patient with the importance of gaining emotional insight. It is necessary not only because confidence in the physician is an important factor and such confidence can only be developed on the basis of emotional contact but also because of the fact that in the development of such symptoms the mechanism of conditioned reflexes plays an important role. By this we mean that certain quite indifferent situations may have been rendered specific because they have occurred under states of emotional stress and in relationship to certain people in the environment of the patient. With the development of an emotional contact with the physician the patient comes to identify the physician with these persons thus actually reliving these experiences but because of the more sympathetic attitude of the physician the painful concomitants are absent and the pattern is broken.

**Eradication of Causative Factors**—In this manner the understanding of the relationships and the emotional reliving of the expe-

riences lead the patient to see his problems more clearly and, therefore, enable both the physician and the patient to plan a way of dealing with them which is more satisfactory than the symptom complex. This introduces us to the third goal of our procedure, namely, the eradication of causative factors. It is quite obvious that symptoms may frequently develop in relationship to situations such as an irritating family relation or a frustrating economic setup, which in themselves may be largely responsible for the illness. Such conditions, which were found especially frequently in some of the psychosomatic disturbances in recently released veterans who were forced to adjust themselves to unsatisfactory jobs or nagging in laws, could not be ameliorated purely on the basis of understanding the relationships of these conditions to their symptoms. One must in addition to that find some way of removing the irritation. It is true that a proper understanding may facilitate a cure of a given symptom, but with the cause still at work, other and perhaps more distressing symptoms may appear. Here we must also keep in mind the question of physical factors such as low states of nutrition, inflammatory conditions, deficiencies and other conditions which help in keeping the patient at a low level of resistance and render him less likely to adjust to his problems.

**Emancipation or Maturation**—Finally, we come to the last goal of treatment of this type which is that of emancipation or maturation. Most physicians are familiar with the fact that the strong interpersonal relationship which is developed between the patient and his physician, the dependence which the patient quite naturally develops upon the physician or the therapeutic setting such as a hospital, are frequently difficult to break at the end of the treatment. The more the physician delves into the personal problems of the patient the more likely the patient is to develop such a dependence and retain it. At the same time it is also quite clear from what has already been said that the development of psychosomatic conditions is very closely tied up with a failure on the part of the patient to mature psychologically and be able to deal with his problems in a grown up fashion. In such a case the dependence which the patient develops upon the physician is frequently of the nature of the attachment of a child to his parents or others on whom he was dependent. It is obvious that curing the patient's symptoms without making the patient independent of the therapeutic setting is not going to produce the desired results. Early in the course of the treatment the physician must gradually prepare the ground for the patient to be able to break away from that dependence and adjust himself on his own resources.

These then are the goals of psychotherapy. It is obvious that the

adequacy of achievement will vary in degree. Perhaps under no circumstances, no matter how complex a method we use, are these goals attained to perfection. At the same time, however, it is not altogether necessary to do that. Frequently the actual exciting causes are so near the surface that the understanding of the immediate factors comes fairly easily. Although we do not mean by that that the physician or the patient has attained a complete understanding of the mechanisms, nevertheless, the insight gained is sufficient to demonstrate some of the relationships between the symptoms and their causes and also to give the physician an opportunity to help the patient in the solution of his problem.

### PSYCHOTHERAPEUTIC TECHNIQUES

The techniques that are available in the practice of brief psychotherapy can be discussed under the headings of *Exploration*, *Emotional Participation* and *Maturation and Emancipation*.

**Exploration**—By exploration we mean the method or methods whereby the material is obtained both from the patient and those about him. So far as the physician is concerned he is in a position to use this method most advantageously with the patient himself and this is done on the basis of appropriate interview technique. In the above discussion we have already indicated the fact that the act of obtaining the material from the patient is important not only for the purpose of getting information but also for the attainment of the other goals. It is while the patient and the physician discuss the patient's problems that emotional contact is established, that the plans for removing causes are made and that the first steps towards eventual emancipation are being taken. This means that the technique of interviewing a patient of any type but particularly one where psychotherapy is contemplated is the most important tool in this procedure. It should be strongly emphasized in the teaching of medical students, interns and residents. For an adequate discussion of this subject we must refer the reader to more extensive presentations in the literature but a few points might be mentioned as highlights in the technique of interview.

The first and perhaps most important feature is the fact that the material which is obtained in the interview must obviously come from the patient and not from the physician. It means, therefore, that the patient should be allowed to express himself and direct questions should be reduced to a minimum. No suggestions should be made and no forced explanations. In fact, if the physician has to err one way or the other, the old dictum of "the less said the better mended" should be followed. It may mean a little more time and more stress on the physi-

cian's patience. In the end, however, it will pay dividends. It is true that the physician must have a certain amount of necessary information which he can only get by direct questioning. Thus he must gain an understanding of the onset, the attending circumstances and the chronology up to a certain point. To that extent it means that direct questions at least at the beginning are indicated, but these should be spread out over the interview at suitable intervals, for the rest of the time he should allow the patient to set the pace. The physician obviously must be on the look out for the cropping up of important relationships and he should make mental notes concerning these points. Taking notes while the patient is talking may be considered by some as essential but it certainly has its disadvantages. It makes the interview somewhat artificial. It reduces the possibility of the proper emotional setting. It frequently causes the patient to worry whether somebody will read these notes and consequently frequently throws them into a quasi legal terminology.

Quite frequently the problems which have led to the development of the symptoms may be partly or wholly repressed by the patient and, therefore, certain means may have to be taken to help the patient to get at this hidden material. The various more complicated forms of psychotherapy and particularly psychoanalysis have given us some rather valuable techniques with which to get at such material. Slips of the tongue frequently indicate contents which are important to the patient but of which he is not aware. One patient with hypertension, for instance, in speaking of his employer frequently tended to use the word *father* instead of *employer*. As the interview progressed it was found that, having grown up under the domination of a strict and rejecting father, the patient has then carried over the attitude of resentment towards his employer and with it the fear of expressing his protests against him.

Somewhat more complicated but still within the scope of brief psychotherapy is the utilization of dream material. It is important to appreciate that the content of the dream frequently deals with repressed material and, therefore, is disguised when the patient wakes up. It is important to encourage the patient to bring his dream material to the physician and in the dreams pick out various points which one then asks the patient to talk about. In using both slips of the tongue and dream material during the interview it has been found extremely valuable to avail oneself of the method of expression which the psychoanalysts refer to as "free association" by which is meant the following procedure. When the word that comes up as a slip of the tongue or as an apparently unintelligible part of a dream, is given to the pa

tient he is asked to tell the physician what comes into the patient's mind without worrying as to its relevance, correctness or any other consideration that would make the patient control the words he brings forth. A great deal of material may thus come out which may appear to be of little importance but eventually the underlying conflict may thus be reached.

With material that is not too deeply buried under the surface which nevertheless is not available to the patient in an ordinary interview, a great deal of help can be obtained from the use of certain drugs that facilitate expression. Sodium amytal or sodium pentothal in dosages of anywhere from  $3\frac{1}{2}$  to 7 or even 10 grains intravenously have been proven of great help in this regard. When the patient has particular difficulty in bringing up material which is very unpleasant such as the experiences of the soldiers under combat, an injection of this drug not only clears away the difficulty in expression but will also lead to easier contact and deeper emotional response to the physician.

**Emotional Participation.**—The use of the drug in facilitating verbal and emotional expression leads us to the next step in the consideration of technique, namely the means employed to secure emotional participation. Perhaps the one most important item to consider here is that of the creation of a setting in which the patient has the greatest possible confidence in the physician. The establishment and maintenance of this relationship requires a good deal of self-discipline and control. The physician must follow rigid rules of honesty as far as the patient is concerned. He must not under any circumstances reveal confidences that the patient has expressed other than by permission of the patient. In order to feel free to bring up personal material the patient must have the complete assurance that it will remain between him and the physician. The physician must also be sympathetic, by which is meant that he must not spoil the patient or express pity for him, but must be earnest and sincere in dealing with problems that the patient brings up. He must refrain from ridiculing the patient or sermonizing to him.

At the same time, however, he must be objective in urging the patient to work hard in an effort to understand how his problems have developed and what issues he must meet if he is to act like a grown-up person. He must not at least early in the treatment inject himself as a person into the procedure. The habit which some physicians have of discussing with the patient their own (physician's) problems, or setting themselves up as a paragon of good adjustment are definitely not



be kept to the subject matter as much as possible. Where problems come up that must be dealt with in terms of removing some causative factors it is best to allow the patient to express his own plan of doing so. He can be steered but should really plan his own solutions wherever possible. There are times when this is not easily attainable by the patient himself. It may be a matter of the patient's intelligence not measuring up to the complexity of the problem, or there may be a need for the intervention of persons or agencies who could help in carrying out this procedure. Under such conditions counseling is indicated, but this should be carried out only to the degree that is absolutely necessary. The more independence the patient is given the better, obviously, the results.

**Use of Allied Disciplines**—This leads us to the discussion of a point that was mentioned early in the introduction, namely, the utilization in the methods of therapy of members of allied disciplines. Perhaps the most useful and also the most logical of these is the *social worker*. Here we might digress a moment to discuss a point essential in understanding the role of the social worker. Most physicians who have had experience in this work know that the emotional relationship that is established in the process of such treatment is not entirely one-sided. Obviously the patient is suffering and he is grateful to the physician for the help and sympathy that he gets but the physician, too, as he works with the patient becomes emotionally involved and invariably finds himself viewing the situation through the eyes of the patient, likes and dislikes, anger or approval and other emotions are quite frequently taken over by the physician through the medium of the patient's attitudes. It is obvious, therefore, that the physician cannot usually see the actual social situation in as unprejudiced and objective a manner as he should as long as he is really interested in his patient. The social worker represents society, its needs, its demands, and also the consideration it deserves. Such a person can present the social setting and help in the evaluation of its importance much more adequately than the one who is treating the patient. At the same time, the social worker through training and experience and contacts has the ability and the time and connections to evaluate plans for readjustment, consider the possibilities of eradication of certain causes and deal with the patient's environment in a much more effective manner. Under certain circumstances, which unfortunately occur quite frequently, social workers are not available and the physician in his education should gain a good understanding of the function and technique of social work. He can then try to carry out his own social work to the best of his abilities or he can enlist the aid of the minister, the good neighbor or the relatives to act in that capacity.

Another important discipline that has developed within recent years is that of *clinical psychology* and it has made some excellent contributions to the understanding of medical problems and the techniques of dealing with them. Tests of an objective nature have been developed which measure personality functions—intellectual as well as emotional. Some of these tests such as the projective techniques (Rorschach and Thematic Apperception Test) also offer good possibilities for uncovering certain problems which are otherwise inaccessible. Here too, and perhaps even more than in the case of the social worker, there are not enough well-trained clinical psychologists for use in all of these problems. Wherever possible studies by clinical psychologists should be incorporated in the treatment of problems of this type. They will not only make the treatment more effective but they will also frequently cut down very materially the time consumed. At the same time, however, it is important for the medical man during his educational career to learn as much as possible about the implications of this work and to some extent the techniques that are used.

**Maturation and Emancipation**—We finally come to the discussion of the methods that can be used in attaining the last of the goals mentioned above, namely that of maturation and emancipation. It is at times a most difficult and at the same time a most important matter for consideration. In a way, just as in all of these techniques and goals, the initial steps towards emancipation must be taken at the beginning of treatment. For instance, letting the patient proceed at his own level and pace in the understanding of the problem, offering a minimum of interpretation and suggestion and letting the patient make his own plans for dealing with his problems produce a good background for the subsequent emancipation of the patient. The less the patient is spoon-fed at the outset the quicker he will grow up in his adjustment at the conclusion.

Great care must also be taken to act judiciously at the time when it is considered appropriate to cease the treatment. On the one hand, it is not advisable to break it off suddenly. If the patient is being seen twice or three times a week, for instance, the weaning process must proceed by a gradual cutting down of the frequency of the visits. At times the patient himself may urge the physician to stop the treatment suddenly, but this should not be permitted. On the other hand, when the time has come this weaning process must be started, regardless of whether the patient will try in one way or another to induce the physician to see him more frequently. It is well at this time to allow the patient more independence in dealing with everyday problems as they come up, actually urging him to do so. Here too, the help of the social worker may be of the utmost importance in that the physician can arrange to

have her see the patient occasionally and let the patient discuss his problems with her. In that way a transference of the patient's dependence upon the physician can gradually be re-directed to the outside through the mediation of the social worker.

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In conclusion, I wish to repeat that the present statement is only a sketchy and admittedly incomplete description of brief psychotherapy. It is hoped that it may serve as a stimulus for further thought and study of the subject.

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## PENICILLIN IN THE TREATMENT OF PULMONARY INFECTIONS

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The advent of the sulfonamides and antibiotic agents in readily available quantity at a price within the reach of all has led to the treatment without definite bacteriologic diagnosis of many cases of obscure infections and illnesses with fever for want of other effective measures. The bacteriologic specificity of these agents however has made clear the necessity for more rather than less precise bacteriologic diagnosis if proper treatment is to be applied. The alteration of bacterial interrelationships by eradication of bacteria sensitive to a given agent may encourage the appearance of infections due to other types of bacteria which remain and flourish. The phenomenon of adaptation to chemiotherapeutic agents with the appearance of resistant bacteria suggests the importance of accurate bacteriologic diagnosis. This must be followed by treatment with adequate dosage for periods sufficient to bring infections well under control rather than treatment inadequate in these respects which serves to confuse the clinical picture and make future therapy and prognosis difficult. The purpose of this paper is to discuss the application of the available penicillin preparations to the treatment of pulmonary infections.

### PENICILLIN IN PNEUMONIA

The effectiveness of penicillin in the treatment of pneumococcal pneumonia has given rise to its widespread use in pneumonia of all types on purely clinical grounds without precise bacteriologic diagnosis when patients are not severely ill and particularly when hospitalization is not necessary. Such a program frequently is successful and the pneumococcus is still responsible for over 90 per cent of pneumonias. Particularly in seriously ill patients other bacteria notably the staphylococcus, beta hemolytic streptococcus and *Klebsiella pneumoniae* (Friedländer's bacillus) may be etiologic agents in which event important differences in therapy will be indicated.

**Pneumococcal Pneumonia**—Successive reductions in the mortality rate from this infection have occurred following the introduction of

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serum, sulfonamides and penicillin. The clinical response and incidence of complications in patients treated with penicillin are quite similar to that following sulfadiazine therapy. The higher incidence of toxic reactions with sulfadiazine, the difficulty in maintaining satisfactory urine output in severely ill patients who may be in shock, in the aged, and in patients with congestive heart failure, and the ineffectiveness of sulfonamides in the presence of accumulations of purulent exudate have made penicillin the agent of choice. Furthermore, only rarely can any advantage be anticipated by combined therapy with both agents. The prompt treatment of pneumococcal pneumonia with either sulfonamides or penicillin significantly decreases the incidence of complications such as empyema, endocarditis, arthritis and meningitis.

A dosage of 20,000 units every four hours for the first twenty-four to forty-eight hours followed by 15,000 every four hours will be effective in almost all cases. Evidence is accumulating that a four-hour dosage schedule is adequate for parenteral penicillin administration and it is well to remember that a daily dose of less than 100,000 units produced extremely good results during the period when penicillin was available in only small quantities.<sup>1</sup> When frequent injections of penicillin are not feasible larger doses may be given at longer intervals. Thus, 100,000 units at eight-hour intervals has been followed by excellent results in a small number of cases in which it has been tested. This is illustrated by the following case history.

CASE I—A 63-year-old white man entered Evans Memorial with the chief complaint of chills and fever of two days' duration. Except for an upper respiratory infection of three to four weeks' duration the patient had been in good health until two days prior to admission when he was awakened from sleep with a shivering chill and feeling of marked feverishness. The day prior to admission there appeared marked general aching, severe cough productive of small amounts of blood-tinged sputum, and severe hiccoughs.

On admission to the hospital, examination revealed a temperature of 102.6° F., pulse 110, respiration 28, and blood pressure 150/80. The essential positive physical findings were limited to the chest where over the entire right lower lobe posteriorly there was dullness to percussion, increased rattle fremitus, whispered pectoriloquy and egophony. A moderate number of moist rales were present over this area. Slight cardiac enlargement was present with a soft blowing Grade II apical systolic murmur. Urine showed a specific gravity of 1.028, 1+ albumin and two to three hyaline casts per high power field. Hemoglobin was 15 gm., white count 15,650 with 94 per cent polymorphonuclear neutrophils, nonprotein nitrogen 45 mg. per 100 cc. blood culture negative. Chest x-ray revealed the right lower lobe to be almost completely and homogeneously consolidated.

Treatment consisted of hydration penicillin 100 000 units every eight hours, and control of hiccoughs by inhalation of 5 per cent carbon dioxide in oxygen and Hnffmann's anodyne. Temperature returned to normal by crisis on the second hospital day and remained essentially so except for occasional rises to  $99.2^{\circ}\text{F}$  during the first seven hospital days following which the temperature remained normal throughout the remainder of the patient's hospital stay. Urinary abnormalities and nitrogen retention rapidly disappeared as did hemoconcentration and the white count returned slowly to normal. Chemotherapy was continued for seven days.

The patient was discharged on the eleventh hospital day. The lungs were entirely clear except for slight decrease in breath sounds over the right chest interpreted as being due to thickened pleura and chest x-ray showed only slight increase in bronchovascular markings over the lower right lung field.

Penicillin in peanut oil beeswax mixtures is also a satisfactory method of circumventing frequency of injection. Injection once daily of 1 cc containing 300 000 units will prove adequate in most cases. Whereas the peanut oil beeswax mixtures contain a suspension of sodium or potassium penicillin G a sesame oil suspension of the procaine salt of penicillin has recently been prepared which is even more satisfactory in the maintenance of prolonged and uniform blood levels and permits the elimination of beeswax from the suspension. This latter preparation is easily administered in the same manner as the peanut oil beeswax mixtures, although the tendency of the procaine penicillin now available to form crystalline aggregates requires attention to certain details to facilitate ease of administration. The bottle must be shaken vigorously for several minutes the material withdrawn and administered at once. The local reaction to procaine penicillin suspension is even less than to peanut oil beeswax preparations. The possibility of procaine sensitivity should be borne in mind when employing this substance which may be given in the same dosage as peanut oil beeswax mixtures. In general however these methods should be used for the less seriously ill patient without coexistent disease. The response to penicillin is prompt in most cases with a crisis occurring within twenty-four hours in over 50 per cent and in forty-eight hours in over 75 per cent. Fever may continue at lower levels for several days. Pneumococci can only rarely be recovered from the sputum twenty-four hours after initiation of therapy and bacteremia responds with equal promptness unless a complication such as endocarditis exists. Treatment should be continued until complete subsidence of the acute symptoms and for two or three days of normal temperature. The total duration of treatment in uncomplicated cases is usually six or seven days.

In patients who are not desperately ill and in whom no serious co-existent disease exists oral administration of 100 000 units every four hours may be employed with an initial dose of 200,000 units, this dosage conforming to the usual 5:1 ratio necessary to produce serum penicillin levels with oral administration comparable to those following intramuscular injection. Absorption of penicillin from the gastrointestinal tract proceeds most efficiently when the drug is administered on an empty stomach, consequently doses should be given insofar as possible about one hour prior to or two hours after meals. The clinical response, incidence of complications and fatality rate in properly selected patients treated in this manner corresponds closely with that in patients treated parenterally.

The excellence of the results obtained with penicillin should not obscure the importance of adjuncts to chemotherapy. The use of oxygen, control of pain and anxiety, maintenance of fluid and electrolyte balance and treatment of co-existent disease are to be carefully observed. It is well to remember that the same factors influence the results obtained with penicillin as determined the outcome prior to chemotherapy and that most of the deaths still occur in the elderly, in chronic alcoholics and in patients with co-existing disease of the liver, kidneys and cardiovascular system. Although chemotherapy has produced a decrease in the case fatality rate it still remains comparatively high in these groups. This emphasizes the need for prompt, vigorous chemotherapy and attention to these co-existing diseases.

**Streptococcal Pneumonia**—Although pneumonia due to the beta hemolytic streptococcus is relatively infrequent it is responsible for a severe, rapidly progressive type of disease usually beginning with pharyngitis and tracheobronchitis, often in young adults. It sometimes assumes almost epidemic proportions during outbreaks of virus infections (measles, influenza) or scarlet fever and is associated with a high mortality rate. These cases occasionally respond poorly to sulfonamides. Doses of the same order of magnitude may be employed in the treatment of streptococcal pneumonia as in pneumococcal pneumonia, but the duration of treatment should be somewhat prolonged because of the greater frequency of purulent complications such as lung abscess and empyema. Thus, a dose of 15 000 to 20,000 units every four hours should be given until a good clinical response is obtained and the temperature has been normal for about one week. In the presence of complications, chemotherapy must be continued for several weeks. The results obtained in this infection are governed more by the duration of therapy than the dosage employed inasmuch as even low dosage will produce cure in a high percentage of cases, whereas short periods of treatment

even with high dosage result in an increased frequency of relapse and purulent complications.

**Staphylococcal Pneumonia**—Whereas the sulfonamides represented a major advance in the therapy of pneumococcal and beta hemolytic streptococcal pneumonia the results following their use in staphylococcal pneumonia were less striking. Penicillin is unquestionably the agent of choice in staphylococcal infections being much more effective than the sulfonamides but likewise less dramatically so than in infections due to the pneumococcus and streptococcus. The staphylococcus is more resistant in vitro to penicillin and resistant strains arise with greater ease in vivo. The more favorable response to chemotherapeutic agents of infections which pathologically are of a diffuse cellulitic type is well known and the marked tendency in staphylococcal infections to necrosis of tissue with formation of localized collections of exudate is another barrier to successful therapy. Staphylococcal pneumonia characteristically shows a confluent type of bronchopneumonia with formation of peribronchial abscesses from destruction of alveoli which progressively coalesce to form larger collections of necrotic tissue. This emphasizes the importance of early diagnosis so treatment may be initiated while necrosis of tissue is at a minimum rather than late when all chemotherapy can accomplish is limitation of the invasive characteristics of the infection leaving purulent complications necessitating either prolonged medical treatment or surgical interference.

Treatment must be intensive both because of the higher order of resistance of staphylococci as well as the fulminant character of many of the cases. A dose of 50 000 units every four hours should be employed and continued until the signs of acute illness subside and temperature returns to normal when it may be decreased to 25 000 to 30 000 units every four hours. Staphylococcal infections differ distinctly from pneumococcal infections which respond to relatively brief periods of treatment and therapy should be continued for at least ten to fourteen days after the temperature is normal because of the longer period of time necessary for healing of necrotic foci. Penicillin administered by aerosol may be of value in hastening recovery particularly if tracheobronchial lesions are present. The concomitant use of sulfonamides has been advocated by some especially early in the course of the disease when tissue necrosis and exudate formation is minimal. If sulfonamides are employed the blood level should be maintained at 12 to 15 mg per 100 cc., which will usually necessitate a dose of at least 1.5 gm of sulfadiazine every four hours.

The response of staphylococcal pneumonia to penicillin is less dra-



matic than in the case of pneumococcal pneumonia. Fever subsides more slowly in these cases with about one third of the patients running a febrile course during the entire first week of treatment. Sputum and blood cultures also are not sterilized so rapidly as in infections due to other gram positive cocci. The poorest results are observed in patients who are elderly, in whom bacteremia is present, particularly if of relatively long duration, and in whom endocarditis or serious coexistent disease of other systems is also present. The importance of early diagnosis is emphasized by the finding that most of the deaths occur in patients who present evidence of overwhelming infection and who are almost moribund before penicillin is started. The frequent occurrence of naturally resistant staphylococci emphasizes the importance of laboratory determination of penicillin sensitivity in order to be certain of adequate dosage. Likewise, since it has been estimated that resistant staphylococci develop in approximately 20 per cent of infections, increased dosage should be considered if the clinical response is not good or if positive cultures persist in the blood or sputum.

**Primary Atypical Pneumonia**—The only treatment of importance in this type of pneumonia without complications is symptomatic and supportive. Administration of chemotherapeutic agents does not shorten the course of the disease and it is very doubtful whether it decreases the incidence of complications. Although some disagreement exists, the general consensus of opinion is that sulfonamides and penicillin are of value only in the presence of complications due to secondary bacterial invasion. Penicillin, or other chemotherapeutic agents depending on the character of the sputum, should be employed if there is evidence of secondary invasion by pyogenic bacteria. Change in the type of febrile response, appearance of purulent sputum with large numbers of gram-positive cocci, appearance of or increase in leukocytosis, or x-ray evidence of spread or massive involvement constitute justification for use of penicillin. If the reasons for starting chemotherapy have been justified, improvement should usually occur in twenty-four to seventy-two hours. The dosage and duration of treatment should be governed by the criteria set forth previously depending on the predominant organism in the smear or culture of the sputum.

**Bronchopneumonia**—Although this type of pneumonia may occur as a primary infection, it is more often secondary to other infections, chronic debilitating illness, or following pulmonary infarction. Either gram-positive cocci or gram-negative bacilli may predominate in the sputum but the former are more common in patients who have not been treated previously with penicillin. Consequently, this agent finds a wider field of usefulness in controlling these infections than other

agents. Again dosage and duration of treatment should be governed by the predominant bacteria.

### PENICILLIN IN EMPYEMA

The early diagnosis and penicillin treatment of pneumonia has decreased the incidence of empyema to about 1 per cent. Sulfonamides may prevent the development of empyema when employed early but once the condition is established these drugs possess little curative value and may even contribute to the production of atypical and localized empyemas which present complicated and difficult therapeutic problems. Penicillin however has made it necessary to re-evaluate the indications for surgical treatment, the well-established principles of which will not be discussed here. Medical treatment alone will be followed by cure in 50 to 65 per cent of patients depending on whether the empyema is putrid or nonputrid, the size and character of the empyema cavity, the viscosity of the exudate and the type of treatment. Among the various pyogenic cocci little difference in response has been observed but cure of putrid empyema due to predominantly anaerobic bacteria is obtained considerably less frequently by chemotherapy alone.

The principles of treatment of empyema are similar regardless of the bacteria involved. Combined systemic and local (intrapleural) therapy is of paramount importance, considered singly the latter is superior to the former. No correlation exists between systemic dosage or duration of treatment and final results. Patients who are treated by the intramuscular route alone with no surgical interference frequently fail to improve or do so only temporarily with relapse as soon as intramuscular penicillin is discontinued. Intramuscular treatment is indicated as long as bacteremia or the active disease responsible for the empyema is present. When control of these features has been attained systemic therapy may be discontinued and local treatment only continued. Occasionally cases will be seen which present quite small collections of pleural fluid in which intramuscular treatment is sufficient to prevent progressive accumulation of exudate and in which resorption of exudate occurs without thoracentesis. Likewise small sterile nonpurulent effusions are observed occasionally following penicillin treatment of pneumococcal pneumonia.

Penicillin is absorbed slowly from empyema cavities; consequently high levels may be maintained for several days in the empyema fluid and demonstrable blood levels may persist for twenty-four hours after intrapleural injection of doses over 100,000 units. The method of treatment and intrapleural dosage will vary somewhat with the type of empyema (nonputrid or putrid) and size of the cavity. When the in-

fection is due to the usual pyogenic bacteria (pneumococcus, beta hemolytic streptococcus, alpha hemolytic or nonhemolytic streptococcus staphylococcus) 50,000 to 100,000 units in a concentration of 5000 units per cc may be employed for small empyemas, although with a large cavity 200,000 units or more should be given after aspiration of exudate. The volume in which the penicillin is given should approximate one third of the exudate removed. If the exudate is quite thick, gentle irrigation with small amounts of saline may facilitate removal of the purulent material prior to instillation of penicillin. This procedure should be repeated at twenty four hour intervals to obtain as complete removal of pleural exudate as possible, although later in the course of treatment thoracentesis may be repeated at forty eight hour intervals. Efficient removal of exudate is a most important aspect of treatment and many of the failures of medical therapy are based on inability to drain the empyema properly because of thickness of exudate or fibrin masses which plug the thoracentesis needle. Removal of volumes which vary widely from day to day usually indicates failure to drain the pus effectively via thoracentesis needle. Of the cures with medical treatment alone the majority will recover in two or three weeks. If cure has not been obtained in three or four weeks surgical measures are usually indicated.

Initiation of proper penicillin treatment of pyogenic, nonputrid empyema generally produces a rapid decrease in respiratory difficulty and toxemia with either a rapid or gradual subsidence of fever. The response may be particularly dramatic in empyema due to the beta hemolytic streptococcus in which marked toxemia is so characteristic. The exudate which is removed should be cultured every time it is removed so the presence of resistant bacteria may be detected, although cultures may remain positive for several days after institution of therapy which eventually results in cure. The problem in treatment, thus, becomes repeated thoracentesis for removal of exudate and administration of penicillin, rather than control of an acute infection.

Although penicillin has altered somewhat the management of the putrid type of empyema associated with marked systemic reaction and varying degrees of peripheral vascular collapse early surgical operation is usually indicated in spite of the dramatic improvement which frequently occurs with penicillin. It is well known that in addition to the fulminant, rapidly progressive type of putrid empyema resulting from the rupture of a lung abscess into the free pleural space, there is a less acute more slowly progressive type resulting from a slow leak from areas of subcortical pneumonitis usually associated with bronchiectasis. In the course of the latter type pleural adhesions have arisen

preventing dissemination of contaminated material throughout the pleural space. Putrid empyema which is recognized early or which does not progress rapidly may respond quite satisfactorily to repeated thoracentesis and intrapleural penicillin. The impressive response which may occur even in the fulminant type of putrid empyema following chemotherapy suggests some re-evaluation of surgical therapy. In spite of considerable clinical improvement following thoracentesis and penicillin surgical drainage has almost always been deemed advisable. Patients need not be operated on however as an emergency procedure and may be in considerably better condition to withstand surgery following the clinical improvement from conservative therapy. It has frequently been possible to perform less radical procedures and the post operative course has been smoother with the application of intramuscular and intrapleural penicillin. In addition to intramuscular doses of 50 000 units every four hours thoracentesis should be performed at eight hour intervals instilling 500 000 units of penicillin intrapleurally following the withdrawal of as much exudate as possible. After twenty four hours of this treatment during which considerable clinical improvement will appear if it is to occur surgical drainage should be instituted if the exudate continues to be foul. Areas of cellulitis and thoracic wall abscesses at the site of insertion of the thoracentesis needle which formerly occurred frequently have become rare with the employment of penicillin.

The best results in the treatment of empyema will be obtained only by careful consideration of the several factors which make it necessary to supplement medical with surgical therapy. The development of a thick walled chronic empyema cavity is the feature to be guarded against. Drainage of an empyema during its early stage by resection of a small portion of rib is a considerably less formidable procedure than the much more radical plastic procedures necessary when application of surgical measures is unjustifiably delayed. It is reasonable to persist in medical treatment as long as symptomatic improvement occurs fever decreases or remains normal the amount of exudate aspirated and size of the empyema cavity decreases and the pus remains sterile. If medical treatment for a period of two or three weeks has not produced cure and if marked improvement is not continuing additional surgical measures should be considered. Although a rib resection at this time lengthens the period of convalescence it prevents the development of a chronic empyema cavity. Repeated removal of extremely thick exudate may become difficult or impossible or flocculent masses of fibrin may develop which plug the thoracentesis needle. Loculations of exudate may appear which cannot be drained efficiently by

thoracentesis. Rapid and repeated reaccumulation of large amounts of sterile fluid make thoracotomy necessary as does evidence indicating the presence of bronchopleural fistula. Marked thickening of the parietal or visceral pleura may make thoracentesis inefficient.

With the advent of chemotherapeutic agents the clinical picture of empyema has been altered in some cases. Following adequate penicillin treatment of pyogenic pulmonary infections some patients will appear to recover completely but, one or two weeks following the cessation of chemotherapy, will manifest the symptoms and physical signs consistent with acute empyema. Such empyemas usually respond well to surgical drainage and the fluid obtained therefrom is usually sterile although positive cultures may occur. This is typified by the following case.

CASE II—A 63 year old white man entered the Massachusetts Memorial Hospitals with a chief complaint of chills, fever, and dyspnea of one week's duration. Five weeks prior to admission the patient experienced an illness characterized by a preceding upper respiratory infection, chills, fever, right chest pain of pleuritic type, and cough productive of mucopurulent sputum occasionally streaked with blood. In addition to symptomatic therapy 800,000 units of penicillin in peanut oil and beeswax was administered daily for a period of ten days at which time all symptoms had subsided, and he gradually resumed normal activity. About ten days later and one week prior to admission he noted increased fatigability and dyspnea on slight exertion, gradually increasing fever, and reappearance of right chest pain.

Physical examination revealed a temperature of  $102^{\circ}\text{F}$ , respirations 30, pulse 88, and blood pressure 120/80. The essential physical findings were limited to the right chest which showed dullness to percussion below the fourth rib anteriorly and below the fifth rib posteriorly, with dullness in the axilla rising to the posterior axillary fold. Diminished breath sounds and whispered pectoriloquy with decreased tactile fremitus were also present over this area. The urine was normal. The hemoglobin was 12.5 gm, white cell count 32,100 with 78 per cent polymorphonuclear neutrophils. Sputum culture showed alpha and nonhemolytic streptococcus and *Neisseria catarrhalis*. Chest x-ray revealed fluid in the right pleural cavity and capsulated fluid in the right major fissure and an appearance suggestive of atelectasis of the right middle and lower lobes (fig 157). 125 cc of greenish sweet-smelling, very thick pus was removed and 200,000 units of penicillin was instilled by thoracentesis. Culture of this fluid showed no growth in six days. A further attempt to drain this loculated empyema by thoracentesis needle met with considerable difficulty due to thickness of the exudate, and the patient continued to run a low grade febrile course. A portion of the ninth rib was therefore resected in order to establish adequate drainage.

Following operation the patient improved rapidly, symptomatically remained afebrile and drainage from his operative wound gradually decreased. The patient has remained well, his operative wound has healed, and chest

x ray reveals no evidence of pulmonary disease three months after his discharge from the hospital

Other cases may develop sterile empyema during the course of adequate penicillin therapy of the underlying active pulmonary disease

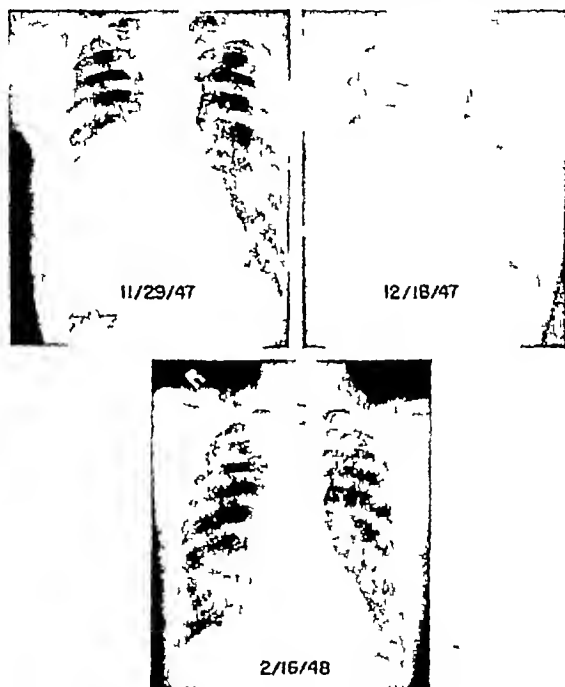


Fig 157 (Case II) 11/29/47 Chest film on admission 12/18/47 Chest film twelve days postoperatively 2/16/48 Chest film two and one half months post operatively

These collections of exudate likewise respond well to surgical drainage. It should be remembered that mere sterilization of pleural exudate is no guarantee of cure inasmuch as prolonged penicillin therapy under such circumstances may result in extensive pleural thickening and accumulation of large masses of fibrin these masses of fibrin are diffi-

cult to remove surgically at a later date and prevent reexpansion of the lung with return of pulmonary function

### PENICILLIN IN BRONCHIECTASIS

This irreversible pathological process involving the bronchial tree and surrounding pulmonary parenchyma has assumed increasing importance in recent years. Better methods of diagnosis have shown it to be considerably more common than previously supposed, and chemotherapy combined with improved thoracic surgical technique has completely changed the method of management of the disease. That the definitive treatment of bronchiectasis is surgical cannot be questioned but only about half the individuals with this disease are suitable candidates for surgery, many of the remaining half showing extensive bilateral disease. Medical measures may provide effective symptomatic relief for a large number of patients ineligible for surgery. The proper use of penicillin and other methods of treatment for pneumonia and sinus infections are important in preventing the development and progression of the changes comprising bronchiectasis and in minimizing hilar fibrosis which increases the difficulty of dissection at the time of surgery.

While defining the importance of penicillin in the management of bronchiectasis the temporary effectiveness should be emphasized. It is most useful in the control of acute respiratory infections associated with varying degrees of pneumonia which are frequent in these patients and for the preparation of patients for surgery. Cough, sputum and general signs of chronic sepsis may be decreased by penicillin treatment during the interval phases although prompt recurrence is not infrequent when treatment is stopped. These features as well as others mentioned below are illustrated by the following case.

CASE III — A 50 year old white man was admitted to Evans Memorial with a chief complaint of productive cough and weight loss since an episode of pneumonia one year prior to admission. One year prior to admission the patient had been treated for pneumonia with intramuscular penicillin for a period of one week with quite a satisfactory response insofar as the acute illness was concerned. During the two months following his discharge he noticed the onset and progressive increase of cough productive of yellowish, occasionally blood streaked foul smelling sputum mostly in the morning. Weight loss of 20 pounds had occurred during the last six months.

Physical examination revealed a temperature of 100.2° F., pulse 82, respirations 22, and blood pressure 130/80. Advanced dental caries and gingivitis were present. Examination of the chest revealed dullness and decreased breath sounds over the right lower lobe posteriorly and posterolaterally and

infrequent coarse rales and rhonchi over both lower lobes posteriorly. The urine was normal. The hemoglobin was 11.7 gm., white cell count 9000 with normal differential, sedimentation rate (Westergren) 120 mm. per hour. Sputum culture revealed hemolytic *Staphylococcus aureus*, *K. pneumoniae*, *H. influenzae* and alpha hemolytic streptococcus. Lipiodol studies revealed bronchiectasis of both bases, in the lingular portion of the left upper lobe and possibly also in the right upper lobe.

In addition to postural drainage 25 000 units of penicillin every three hours was administered intramuscularly as well as an equal amount by the aerosol route omitting two of the doses by the latter route during the night. The patient became afebrile on the third day of treatment and remained so until discharge. The quantity of sputum gradually decreased from an initial volume of 350 cc. to a final volume of 50 cc. after four weeks of this type of therapy. The initially foul sputum became distinctly less malodorous during the course of the treatment. The rales at both lung bases gradually diminished. The sputum culture at the conclusion of treatment showed *E. coli*, *Proteus vulgaris* and *H. influenzae*. The patient was discharged improved and was instructed to use penicillin 25 000 units per cc. four times a day in a Vaponefrin nebulizer.

Approximately three months after discharge the patient returned with increased cough and sputum which on culture revealed *Proteus vulgaris* and *H. influenzae*. A course of streptomycin aerosol failed to produce any clinical improvement or eradication of the gram-negative members of the sputum flora, all of which were shown to be highly resistant *in vitro*.

Postural drainage, bronchoscopic aspirations and general care are not to be neglected.

The importance of administration of penicillin aerosol is well established and better results may be obtained if intramuscular injections are employed concomitantly. Various methods have been described for aerosol therapy.<sup>2-4</sup> The original articles should be consulted for details of techniques.

Two general types of nebulization have been used—that employing a hand-operated bulb or foot pump as a power source and that employing oxygen for supplying the power necessary to break up the aqueous solution of penicillin into a fine mist. Although the hand bulb is readily available and simple it does not produce a fine mist and its use is tiring to the patient.

The Vaponefrin nebulizer, which is manufactured both of glass and of plastic, the latter being nonbreakable, produces a finely divided mist with an oxygen flow of about 5 liters per minute. A valve is essential for regulating the flow of oxygen from the tank. The particles produced by this method are of such size that very few leave with the expired air so that the use of a rebreathing bag is not necessary.<sup>4</sup> Like



wise, apparatus designed for production of negative pressure during a part of each respiratory cycle offers little advantage in the treatment of bronchiectasis although it is of value in therapy of sinusitis. The equipment necessary for this type of therapy is now readily available and applicable for use in the home. Twenty-five thousand units in 1 cc should be aerosolized every four hours while the patient is awake and once during the night if necessary. Fifteen minutes is usually required to nebulize this volume of solution. Small tablets of penicillin are available which dissolve readily and may be dropped through the vent in the nebulizer to which a small volume of saline may then be added, thus obviating the difficulties involved in the use of penicillin in rubber capped bottles. In conjunction with the aerosol therapy, 15,000–25,000 units should be administered intramuscularly every four hours. As improvement occurs, parenteral therapy may be discontinued and aerosol treatment continued with lengthening of the intervals between inhalations so that finally they are being taken once or twice daily.

Following eradication of the penicillin sensitive, gram positive bacteria one frequently observes, particularly in cases showing a poor response to penicillin aerosol, a flourishing population of gram-negative bacilli which in turn may respond to streptomycin aerosol although with considerably less frequency than do the gram positive bacteria to penicillin. Because of this phenomenon and the marked improvement which sometimes follows eradication of gram-negative bacteria the two antibiotics have been employed together for nebulization. Streptomycin may be nebulized with penicillin using 50,000 to 100,000  $\mu\text{g}$  in the 1 cc of solution to be aerosolized. The viscosity of more concentrated solutions results in frequent clogging of the nebulizer and frothing of the solution.

The duration of treatment varies with the effects obtained. Control of acute episodes of pneumonitis is generally relatively rapid but the chronic nature of this disease should suggest that more prolonged treatment is necessary to produce subsidence of the chronic inflammatory process than in the case of acute infections. Thus, while marked improvement with decrease in cough volume and foul character of sputum and increased vital capacity and general well-being may appear after the first week of therapy, some patients may show improvement only after two to four weeks of therapy. The irreversible changes in the bronchial tree predispose to early and frequent reinfection. Patients unsuitable for surgery who are to be treated by medical means alone should be treated for several weeks with repeated treatment at intervals depending on the recrudescence of symptoms. Improvement may be expected in 50 to 75 per cent of patients and by repeated treatment

considerable rehabilitation may be achieved poorer results may be expected in elderly patients with emphysema and fibrosis in which transmission of the aerosol to the site of infection is inefficient To what extent combined penicillin-streptomycin aerosol will improve the results is undetermined Appearance of streptomycin resistant bacteria is quite frequent in contrast to the infrequency of development of penicillin resistant organisms

Use of penicillin as an adjunct to surgical treatment has extended the indications for surgery reduced the incidence of postoperative empyema and by diminishing the amount of sputum preoperatively has decreased the frequency of atelectasis Intramuscular and aerosol therapy should be administered preoperatively until the volume of secretion is at a minimum usually one to three weeks Postoperatively penicillin should be continued until the patient has been afebrile for about five days should removal of pleural fluid be necessary 100 000 units should be instilled following each thoracentesis

Oral reactions to penicillin consisting of edema of the lips stomatitis or glossitis with which the tongue may appear either red or grayish black will be observed with increased frequency if penicillin aerosol therapy is prolonged

#### PENICILLIN IN BRONCHIAL ASTHMA

The results of penicillin therapy in these cases have been almost uniformly disappointing whether the intramuscular or aerosol method has been employed The part which coexistent bronchial infection plays will to some extent probably determine the effect obtained Penicillin sensitive organisms are usually eradicated and large numbers of gram negative bacilli usually appear but little symptomatic relief is obtained The dangers of local or general allergic reactions to penicillin should always be kept in mind Although we have not observed any alarming reactions a number of asthmatic patients have become definitely worse following intramuscular or aerosol penicillin and other investigators have reported the appearance of asthma in patients treated by aerosol who had previously never experienced this symptom

#### PENICILLIN IN ABSCESS OF THE LUNG

The part which penicillin plays in the treatment of lung abscess will vary with the situation peculiar to the individual patient Best results will be obtained only by the judicious application of both chemotherapy and surgical measures Patients who manifest acute constitutional symptoms and signs will usually improve with penicillin with decrease in fever cough sputum general toxicity and pneumonitis surround

ing the abscess. The following case illustrates the favorable response which may occur with penicillin therapy.

**CASE IV**—A 28 year old white woman was admitted to Evans Memorial with the chief complaint of productive cough, chills, and fever of four weeks' duration. Six weeks prior to admission, several days before the delivery of her fourth full term infant, she noted the onset of an upper respiratory infection accompanied by a mild nonproductive cough which persisted until four weeks prior to admission when it became productive of thick, yellow, purulent sputum. Shortly after, chills, fever and left chest pain occurred. Symptomatic therapy produced partial remission of these symptoms although cough continued, as did nightly chilly sensations and sweats. Progressive weakness, weight loss of about 10 pounds, and occasional, faint blood streaking of the sputum finally brought her to the hospital.

Physical examination revealed a temperature of  $103^{\circ}\text{F}$ , pulse 96, respirations 36, and blood pressure 130/80. The essential positive physical findings were limited to the chest which showed slightly greater respiratory excursion on the right and occasional rales to the left of the spine posteriorly with occasional posttussive rales over the left apex anteriorly. The urine was normal. The hemoglobin was 11 gm, white cell count 10,000 with normal differential, sedimentation rate 115 mm per hour and blood culture was negative. Sputum culture revealed alpha hemolytic streptococcus, hemolytic coagulase positive *Streptococcus* and *E. coli*. Smear and culture of sputum was negative for acid fast bacilli. Chest x-ray showed an area of pneumonia at the left apex containing an elliptical cavity approximately 2 cm in diameter with a fluid level (fig. 158).

In addition to symptomatic therapy for cough and chest pain, 20,000 units of penicillin was given every three hours intramuscularly and 25,000 units every four hours by the aerosol route. A decrease in cough, sputum, and chest pain occurred during the first week of penicillin therapy. Febrile rises to as high as  $101^{\circ}\text{F}$  occurred during the first eleven days of penicillin therapy, following which the temperature remained normal. After two weeks of chemotherapy the patient was asymptomatic, producing no sputum, and the chest film showed marked resolution of the pneumonia in the left upper lobe although the cavity was still present but markedly reduced in size. After three weeks of therapy chest x-ray revealed continued resolution of the pneumonia and no cavity could be demonstrated in the left upper lobe. After four weeks of treatment there was no evidence of active pulmonary disease and only slight residual pleural thickening remained. The patient was discharged, convalesced uneventfully, and has remained well during the one and one half years since her discharge.

However, medical therapy should not be continued after it is evident that no further benefit is to be obtained. Mechanical factors are of importance in the results obtained with penicillin. Acute abscesses which drain well bronchially do well. Abscesses which persist with the forma-

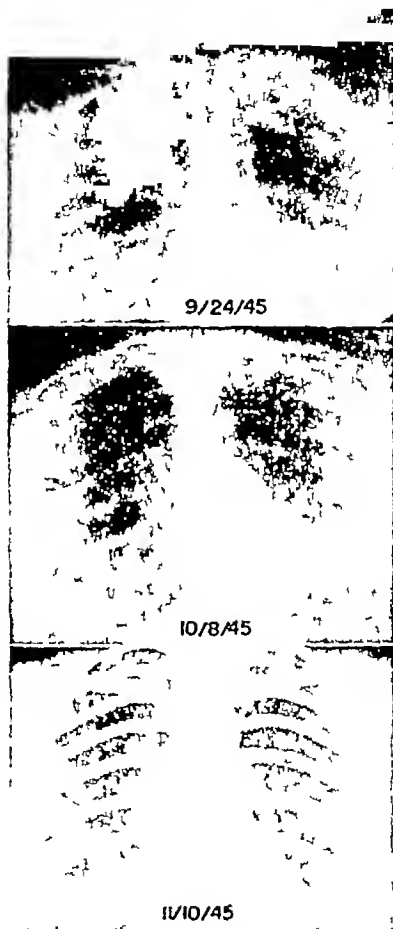


Fig. 19 (Case IV). 9/21/45. Chest film on admission. 10/8/45. Chest film after fourteen days of penicillin therapy. 11/10/45. Chest film two weeks after discharge from hospital.

tion of fibrotic walls which collapse with difficulty cannot be expected to respond to chemotherapy alone. The aerobic postpneumonic type of abscess will frequently respond well, healing completely with chemotherapy alone, particularly if treatment is started within two weeks of the onset of infection and continued until there is x-ray evidence of resolution of the process. This resolution usually requires several weeks and may require months. The anaerobic, putrid abscess arising on the basis of bronchial obstruction and atelectasis responds poorly to chemotherapy and requires surgical drainage. This is well illustrated by the following case.

**CASE V**—A 27 year old colored man was admitted to Evans Memorial with the chief complaint of chronic cough productive of large amounts of foul smelling sputum. Three months prior to admission the patient underwent a tonsillectomy under ether anesthesia. Two weeks later he developed cough productive of sputum both of which progressively increased in severity. Intermittent fever, right chest pain, and 20 pounds weight loss occurred during this period and he was treated in an outside hospital with 30 000 units of penicillin every three hours for a period of three weeks with some decrease in cough and production of sputum but continuation of fever, pain, and no essential change in the x-ray appearance of the pulmonary lesion.

Physical examination revealed a temperature of 102° F, pulse 100, respirations 30, and blood pressure 120/60. The positive physical findings were limited to the chest which showed limited expansion on the right, increased dullness over the superior portion of the right lung to the level of the seventh rib posteriorly and the third interspace anteriorly, with a few scattered rales over the right upper lung field posteriorly. The hemoglobin was 10.5 gm, white count 20,500 with 72 per cent polymorphonuclear neutrophils, sedimentation rate 110 millimeters per hour. Chest x-ray showed a cavity with a fluid level in the right upper lobe.

Adequate open drainage of this abscess was obtained in the midaxillary line following partial resection of the fourth and fifth ribs under local anesthesia. Penicillin was continued postoperatively, adequate drainage appeared to be established and a bronchocutaneous fistula was obviously present. During the three postoperative months marked symptomatic improvement continued but moderate productive cough with a small amount of drainage and evidence indicating a bronchocutaneous fistula persisted. Further surgical intervention was therefore, deemed advisable and lobectomy of the right upper and middle lobes was performed. Following an uneventful convalescence the patient has been entirely well for a period of fifteen months from the final operation.

Although prolonged therapy for weeks or months may be required to produce healing, pursuance of adequate medical treatment for two to four weeks without evidence of definite and continuing improve-

ment should suggest a review of the situation with a view to surgical intervention so that pulmonary damage may be minimized and the least radical procedure may be adopted. Penicillin serves as a valuable adjunct in preventing postoperative empyema and thoracic wall abscess.

Combined aerosol and intramuscular penicillin should be employed with a dosage of at least 25 000 units every four hours by both routes omitting the aerosol during the hours of sleep. Cure should not be assumed without performance of bronchograms inasmuch as residual cavities may be demonstrated by this means which are completely inapparent on routine films. Likewise penicillin treatment can scarcely be regarded as curative if bronchiectasis is present following therapy.

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# USE OF ANTISPASMODICS AND SPASMODICS IN THE TREATMENT OF GASTROINTESTINAL DISORDERS

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Abdominal complaints frequently are caused by uncoordinated and abnormal motor function of the gastrointestinal tract. The symptoms so produced are extremely varied but include diarrhea, constipation, cramps, bloating, flatulence, abdominal distress and sensations of epigastric fullness and pressure. In treating these complaints the physician naturally attacks the underlying causes, but he may also relieve the motor disorders directly by the use of antispasmodics and spasmotics.

## ANTISPASMODICS

**Mode of Action**—Antispasmodics may affect gastrointestinal motor function by one of three basic mechanisms:

1. The activity of the smooth muscle is depressed directly.
2. The action of the parasympathetic nervous system, which on the whole stimulates gastrointestinal motility, is opposed. Since the parasympathetic system is believed to liberate a chemical mediator, acetylcholine, drugs that oppose parasympathetic activity are called *anticholinergic*.
3. The action of the sympathetic nervous system, which inhibits motility, is imitated or potentiated. The chemical mediator of this system is an adrenalin-like substance; hence sympathicomimetic drugs are called *adrenergic*. In actual practice the use of adrenergic drugs is disappointing for the side effects may be marked and adrenergic action on gastrointestinal motor function is often transient and insignificant.

**General Evaluation**—The properties desired in an ideal antispasmodic are:

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- 1 Effectiveness in oral form
- 2 Long duration of action
- 3 Freedom from toxic effects and side reactions
- 4 Absence of habit formation
- 5 Inexpensiveness

In spite of the many preparations on the market, the ideal antispasmodic, as outlined above, is not available at present. One must choose, consequently, the antispasmodics that most closely approach the characteristics of the ideal drug. This choice is anything but easy, particularly because the effectiveness of a preparation can be evaluated by any one of four widely different methods which often yield contradictory results.

1 An antispasmodic may be tested by noting its effect on isolated smooth muscle, such as a strip of intestine or a guinea pig uterus. Effectiveness of a drug as demonstrated by tests of this type is no insurance that the drug possesses any clinical value. The latest super antispasmodic that the physician may be urged to use may relax the uterus of a guinea pig, but it may have very few antispasmodic properties when used in the much more complex situation that obtains in the intact, living animal.

2 The second method which evaluates the effect of drugs in whole animals encounters two difficulties. In the first place, the response of man's gastrointestinal tract to an antispasmodic agent is not necessarily identical with the response observed in an animal. Secondly, laboratory animals often are subjected to operative procedures which make observation of the intestinal response easier but also create unphysiologic conditions.

3 The third method, objective clinical investigation, studies the action of antispasmodics in human beings and employs methods that are as objective as possible. For example, intestinal motility may be observed in a resting human subject by means of fluoroscopy or balloon kymograph records obtained under controlled conditions. Thereupon a drug is given and the subsequent motility compared with that of the control period. A balloon kymograph method<sup>1</sup> was used by us in studying the effect of diverse drugs on the motor function of the normal human small intestine. The results of these studies are summarized in Table I. Such observations, however, permit only limited conclusions. Thus a drug may be ineffectual as judged by balloon kymograph tracings of small intestinal motility, but the possibility remains that the drug may act elsewhere in a manner not detectable by balloon kymograph methods.

4 The fourth method depends upon evaluation of the patient's clinical course. In conditions likely to be treated with antispasmodics such an evaluation is difficult. The evidence is nonobjective and usually rests on the patient's statements. If a patient feels better after he is given a certain preparation it may be the result of this treatment but improvement may be spontaneous, may be psychogenic, and is influenced in general by a host of uncontrolled factors.

**Administration.**—When and how should antispasmodics be given? Although wide variations are to be expected, an antispasmodic given by vein usually is active within a few minutes, an intramuscular or subcutaneous injection in fifteen to thirty minutes, and an oral dose in thirty to sixty minutes. An intravenous injection acts very rapidly, but the total effect and its duration may be less than that achieved by an intramuscular dose, for the high blood levels of a drug that follow its intravenous administration favor partial loss through destruction and excretion. Furthermore, some drugs of which syntropau may serve as an example may be effective if given by mouth but are inactive if given parenterally.

The time and the frequency of giving oral doses should be determined by the chronological characteristics of the patient's symptoms. In patients who complain of cramps and gas soon after eating, for example, the apparently hyperactive gastrocolic reflex should be treated by giving an antispasmodic about thirty to fifteen minutes before meals. If a patient with peptic ulcer complains of pains one hour after meals and during the night, the antispasmodic is logically given just after meals and at bedtime.

In general, patients should be told to use oral antispasmodics at stated times, not as needed. If an antispasmodic works at all, it works by substituting its own type of controlled intestinal motility for the abnormal motility causing the symptoms. This objective can hardly be achieved if medication is used haphazardly and irregularly, and only when the intestinal abnormality is at its maximum.

**Belladonna Alkaloids.**—This group includes atropine, levorotatory hyoscyamine (bellafoline), scopolamine (hyoscine), and tincture of belladonna. These substances act as antispasmodics by virtue of their anticholinergic activity.

The belladonna alkaloids have been used for many years as antispasmodics and have enjoyed a somewhat fluctuating popularity. Today the list of available antispasmodics is larger than ever before, but atropine, levorotatory hyoscyamine, and belladonna remain in our opinion the most effective depressors of intestinal motility that we possess. For this reason we have used, in our studies of small intestinal motility,

TABLE 1

Drug	General Clinical Information			Experimental Data Balloon-Kymograph Records of Human Small Intestine (Drugs Given Parenterally)			
	Dosage	General Evaluation Based on Literature, Tests, and Clinical Impression	Side Reactions	Decrease in Tone 0-4+	Decrease in Peri- staltic and Other Waves 0-4+	Approximate Duration of Effect	Evaluation in Compari- son with Effect of Atropine 0.6 mg (gr 1/100) Atropine sc = 100 %
Atropine	Oral 0.4 mg (gr 1/150) to 0.6 mg (gr 1/100) Parenteral—sc or im Same Dose	Effective antispasmodic Depresses tone and peri- staltic waves	Moderate Dryness of mouth, my- driasis, palpitation	3+	3+	1 1/2 hours	100 %
L-hyoscyamine (Bellafoline)	Oral 0.25 mg (gr 1/240) to 0.5 mg (gr 1/120) Parenteral—sc or im Same Dose	Effective antispasmodic Depresses tone and peri- staltic waves	Moderate Same as atropine	4+	4+	3 hours	150 %
Scopolamine	Oral 0.4 mg (gr 1/150) to 0.6 mg (gr 1/100) Parenteral Same Dose	Insufficient data	Variable May be pronounced	4+	3+	1 hour	100 %

Tincture of Bella donna	Oral 0.6 cc. (min. 10) to 1.2 cc (min 20)	Similar to atropine	Similar to atropine		Not Tested	
Trasentine	Oral 75 mg (gr 1 1/4) to 150 mg (gr 2 1/2) Parenteral—i m or i v 50 mg (gr 5/6)	On the whole less effective than atropine but highly recommended by some authors.	Rare	1+	2+	30-45 min 30%
Syntropan	Oral 50 mg (gr 5/6) to 100 mg (gr 1 2/3)	Tests show little antispasmodic activity but good results reported in clinical trial.	Rare	0	1+	30 min 10%
Homatropine methyl bromide (Novatrin) (Nisoplin)	Oral 2.5 mg (gr 1/25)	Insufficient data	Few		Not Tested	
Papaverine	Parenteral—i v, only 32 mg (gr 1/2) to 64 mg (gr 1)	Has to be given intravenously Transient effect.	Vasodilation Patient should be lying down to prevent syncope	3+ 0	1+ 0	4-6 min 0 75% (i v) 0 (i m)
Profenil	Oral 60 mg (gr 1) to 120 mg (gr 2) Parenteral—i m or i v 45 mg (gr 3/4)	Insufficient data	May lower blood pressure if given parenterally Patient should be reclining	0	0	0

TABLE 1 (Cont)

## ANTISPASMODICS

Drug	General Clinical Information			Experimental Data Balloon-Kymograph Records of Human Small Intestine (Drugs Given Parenterally)			
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Ametheon	Oral 50 mg (gr 5/6) to 100 mg (gr 1 2/3) Parenteral—i m only 100 mg (gr 1 2/3)	Insufficient data	Should be taken after meals. If given i m patient should be lying down as may cause diz- ziness, syn- cope	0	0	0	0
	Oral 125 mg (gr 2) to 250 mg (gr 4)	Insufficient data	Occasional			Not Tested	

<b>Nitrites</b> 1. Amyl nitrite 2. Nitroglycerin	1. 0.3cc (min. 5) by inhalation 2. 0.06mg (gr 1/100) sublingually	Action too evanescent for clinical use except for the treatment of acute spasms such as biliary spasm.	Headache, giddiness, faintness, weakness. Patient should be lying down when amyl nitrite used.		Not Tested •	
Amphetamine (Benzedrine)	Oral 10 mg (gr 1/6) to 15 mg (gr 1/4)	Ineffective in small doses. Large doses do not uniformly depress motility.	Central excitation with such large doses.		Not Tested	
Tetraethyl ammonium chloride (Etonon)	Parenteral—i m or i v 100 mg (gr 1 2/3) to 400 mg (gr 6 2/3)	Good antispasmodic but side reactions limit use.	Postural hypotension produced. Therefore patient should be reclining.		Not Tested	
Dibutyltin	Parenteral—i m. 2 mg (gr 1/30) to 10 mg (gr 1/6)	Preliminary reports indicate good antispasmodic activity.	Insufficient data.		Not Tested	



0.6 mg (gr 1/100) of atropine sulfate subcutaneously to produce a standard effect against which the activity of other drugs is measured. A few drugs are the equal of atropine with respect to the degrees and the duration of its spasmolytic action, but most preparations are decidedly less effective.

If atropine is so outstanding on the basis of tests, why does it not enjoy a better reputation in clinical practice? Partly responsible are the side reactions which attend its use. Normal intestinal motility, or one that is slightly deranged, responds readily to doses of atropine that do not produce major side effects. More severe disorders require larger doses; we have, for example, temporarily arrested the colics of partial intestinal obstruction by giving 0.6 mg (gr 1/100) intramuscularly. Such doses, however, are hardly suitable for routine and continuous use. It appears that atropine and its related substances are good antispasmodics, but their clinical use is limited by the side reactions which follow doses large enough to achieve maximum effectiveness.

*Dosage and Preparation*—It follows from what has been said above that the optimum dose of atropine and related drugs is the largest possible amount which barely produces side reactions. Average doses of this type are presented in Table I, but considerable individual variation exists in the response of patients. In some dosage has to be increased, in others decreased. As a general rule, however, no more than 1.5 cc (minims 20) of the tincture of belladonna or 0.6 mg (gr 1/100) of atropine sulfate, or 0.5 mg (gr 1/120) of bellafoline should be given at a single dose, nor should more than four such doses be given within any twenty-four hour period. Very small doses, such as 0.3 cc (minims 5) of tincture of belladonna, or 0.1 mg (gr 1/600) of atropine have been tried, but they could hardly be expected to prove effective.

Although tincture of belladonna contains other alkaloids than atropine, little evidence supports the concept that a significant difference exists between the antispasmodic properties of these two preparations. Consequently, the choice between tincture of belladonna and atropine sulfate is often decided on the basis of personal preference, price and ease of administration.

*Hyoscyamine*—Atropine is believed to consist of two substances, dextrorotatory and levorotatory hyoscyamine. Of these the levorotatory form is much more active as far as the gastrointestinal tract is concerned.<sup>2</sup> Levorotatory hyoscyamine is available under the trade name bellafoline which, as might be expected, is an effective antispasmodic but also produces atropine-like side effects. It has been claimed that bellafoline produces less side effects than an equivalent dose of atropine, but this claim has not yet been substantiated.

*Side Reactions and Toxic Effects*—Moderate side effects that attend atropinization are inhibition of salivation with consequent dryness of the mouth dilatation of the pupil with blurring of vision and tachycardia. If a patient is sensitive, or if large doses are used restlessness, psychosis and dermatologic lesions may appear. Since many patients who are sensitive to the belladonna alkaloids have had experience with these drugs, their use should always be preceded by questions concerning such sensitivity. In any patient with glaucoma, atropine and related substances are contraindicated.

*Scopolamine*—Scopolamine possesses well-defined antispasmodic properties, which when added to its tranquilizing effects on the central nervous system make it a very useful drug in the prevention or treatment of seasickness. For routine use however scopolamine is not advisable for its side reactions are often extreme and unpredictable. Thus even moderate doses of scopolamine, such as 0.4 mg (gr 1/150) may produce states of confusion or delirium.

*Adrenalin and Amphetamine*—As has been stated previously the theoretical spasmolytic action of adrenalin has little clinical significance. Its action on the gut is evanescent and unpredictable<sup>3</sup> and its cardiovascular effects predominate. Amphetamine sulfate (benzedrine) depresses gastrointestinal motility occasionally but large doses 15 to 20 mg have to be used.<sup>4, 5, 6</sup> The nervous reactions that might follow the repeated administration of such large doses probably contraindicate the use of benzedrine as an antispasmodic. It is possible however that benzedrine in doses of 5 mg may be used beneficially in conjunction with other antispasmodics. Any benefits so derived may be related to the effect of benzedrine on the central nervous system rather than to any spasmolytic action.

*Papaverine and Nitrites*.—Though these drugs are structurally dissimilar they are discussed together since their use is limited to situations where rapid but transient antispasmodic effect is desired. Papaverine is an opium alkaloid but differs from other opium derivatives in that it reduces rather than increases intestinal tone.<sup>7</sup> Given by mouth subcutaneously or intramuscularly it is quite ineffective given by vein it produces a sharp but brief decrease in intestinal motility. The nitrites in the form of nitroglycerine or amyl nitrite produce a somewhat similar effect.<sup>8</sup> For this reason papaverine or the nitrites may be used in the treatment of acute spasms either biliary or gastrointestinal but they are not suitable for the treatment of more chronic disorders. Since both papaverine and the nitrites act as vasodilators the patient should be lying down when these agents are used.

*Synthetic Antispasmodics*.—For many years chemists have attempted to synthesize a drug that retains or exceeds the spasmolytic action of the

belladonna alkaloids on the gastrointestinal tract, but that does not produce undesired side effects on other organs. So far, this attempt has not been very fruitful. Although side reactions have been reduced and even eliminated, a simultaneous reduction in spasmolytic activity has impaired the usefulness of many products that have been synthesized.

*Trasentine and Syntropan*—Two of the best known synthetic antispasmodics are trasentine and syntropan. Although these drugs possess different chemical structures, they act similarly in that both relax the intestine by a direct effect on the smooth muscle, both are slightly anticholinergic, and both exhibit some local anesthetic properties.<sup>8</sup> Their precise status as antispasmodics is still a matter of debate. In our studies on the human small intestine, the spasmolytic action of parenterally administered trasentine and syntropan proved considerably less than that of the natural belladonna alkaloids. On the other hand, three groups of investigators<sup>4, 9, 10</sup> have found that trasentine and atropine induce an approximately equal relaxation of the large bowel in man. Clinical observations, made by competent authorities,<sup>11, 12, 13</sup> also confirm the efficacy of trasentine as an antispasmodic, especially in the treatment of colonic disorders. It appears that trasentine, in spite of our disappointing results, is a useful antispasmodic, particularly since oral preparation of the drug is nearly free of side effects. The evidence with respect to syntropan is more equivocal.<sup>14, 15</sup>

The fact that trasentine and syntropan are mild local anesthetics may contribute to their usefulness in the treatment of gastroduodenal disorders. According to Wolf and Wolff,<sup>16</sup> hyperemia and engorgement lower the pain threshold of the stomach so that ordinarily painless gastric contractions become painful. If this is the case, an agent that acts as an anesthetic might be effective in part by lessening the sensitivity of an irritated gastric lining.

In general, trasentine or syntropan can be used with reason under the following conditions:

1. A patient has received belladonna alkaloids without benefit.
2. A patient is known to be sensitive to the belladonna alkaloids, or is unduly disturbed by moderate side reactions. Some nervous individuals complain bitterly if normal salivation is decreased.
3. A patient with glaucoma who requires antispasmodics.
4. A patient with principally colonic disorders (spastic colon, irritable colon).
5. A patient with gastroduodenal complaints associated with irritation of the gastric mucosa.

*Homatropine Methyl Bromide* (Novatrin, Mesopin).—This com-

pound resembles atropine in structure and in anticholinergic action. It has been shown to depress gastric motility in man<sup>17</sup> and it is relatively free from side effects. Homatropine methyl bromide has also been recommended on the basis of clinical trials<sup>18, 19, 20</sup> but since most of these were uncontrolled the exact value of this preparation is unknown.

*Pavitrine, Profenil, Amethone and Dibutoline*—These are other synthetic substances that have received favorable comment as to their spasmolytic activity.<sup>21, 22, 23</sup> These agents however have been introduced rather recently and their evaluation requires more study. Dibutoline believed to act directly on smooth muscle and also anticholinergically has recently been investigated by Cummins *et al.*,<sup>24</sup> who report relief of painful spasms in a few patients after injections of this drug. Our experience has been limited to amethone and profenil; preliminary investigations indicate that these substances are inferior to the other antispasmodics tested with respect to their action on the human small intestine.

*Tetraethylammonium*—Tetraethylammonium salts either the chloride (etamon) or the bromide have recently been studied as gastrointestinal relaxing agents. These substances have interesting pharmacologic properties in that they block both parasympathetic and sympathetic ganglia. Lyons *et al.*<sup>25</sup> who studied the progress of a barium meal fluoroscopically observed cessation of gastrointestinal motility following intramuscular injection of tetraethylammonium. This observation was corroborated by Chapman *et al.*<sup>26</sup> by means of balloon kymograph studies, but the response was similar and in no way superior to that produced by atropine sulfate 0.6 mg. (grains 1/100) intravenously. After injection of etamon its effect takes place almost immediately and persists approximately thirty to sixty minutes. Postural hypotension which may be distressing occurs frequently and is a definite disadvantage to the use of etamon as an antispasmodic.

*Combinations of Antispasmodics*—A number of preparations on the market contain several antispasmodics often in combination with phenobarbital. These combinations are offered in the belief that the component drugs act synergistically in a more effective fashion than an equivalent dose of a single drug. Such a belief does not appear warranted by the evidence available at present. Unless hypnotic doses are used<sup>27, 28</sup> the inclusion of phenobarbital such as 30 mg. (grain 1½) for example probably does not enhance the antispasmodic properties of any preparation. On the other hand the inclusion of barbiturates in antispasmodic preparations is frequently warranted because the sedative may allay neurogenic impulses that promote disorders of gastrointestinal motility.

TABLE 2  
SPASMODICS

Drugs	Dosage	General Evaluation Based on Literature, Tests, and Clinical Impression	Side Reactions
Acetyl beta methylcholine (Mechoyl)	Oral 100 mg (gr 1 2/3) to 200 mg (gr 3 1/3) Parenteral—s c or i m 6 mg (gr 1/10) to 10 mg (gr 1/6)	Moderately effective spasmotic Limited use because effect of oral preparation unpredictable. Re- sponse to parenteral form intense and of short duration	Sweating, salivation, bradycardia, flushing, abdominal cramps, asthma in susceptible individuals
Carbamiminoylecholine (Doryl) (Lentun)	Oral 25 mg (gr 1/25) Parenteral—s c only 0.2 mg (gr 1/300) to 0.4 mg (gr 1/150)	Effective spasmotic, but use limited because most toxic of choline derivatives	Same as mechoyl. In addition may cause malaise, faintness, nausea and collapse. May be serious
Urethane of beta methylcholine (Urecholine)	Oral 5 mg (gr 1/12) to 10 mg (gr 1/6) Parenteral—s c or i m Same Dose	Promises to be useful cholinergic drug. Increases peristalsis and tone with moderate side effects	Slight salivation and sweating Minimal cardiovascular effects
Extracts of posterior pituitary 1 Pituitrin 2 Pitressin	Parenteral only—s c or i m 5-10 units (1/2 to 1 cc or min 7 1/2 to 15)	Increases peristaltic waves. Short acting	Pallor, increased blood pressure, oc- casional headache, tachycardia
Neostigmine (Prostigmine)	Oral 15 mg (gr 1/4) to 30 mg (gr 1/2) Parenteral—s c or i m 0.25 mg (gr 1/20) to 0.5 mg (gr 1/20)	Increases tone and peristalsis. Com- bines effectiveness with low toxic- ity	Minimal

<p>D, isopropylfluorophosphate (DIFP)</p>	<p>Parenteral—i m. only 1.5 mg (gr 1/40)</p>	<p>Effective in increasing tone and peristalsis but preliminary reports contradictory Not recommended until further information available</p>	<p>Few with doses under 2.0 mg May get anorexia, nausea, vomiting and central nervous system effects.</p>
<p>(Ergotamine)</p>	<p>Oral 10 mg (gr 1/60) Parenteral—i.v. or i.m. 0.25 mg (gr 1/240)</p>	<p>No effect per se on intestinal activity Used to potentiate neostigmine.</p>	<p>Should not be used in patients with peripheral vascular disease atherosclerosis and hepatic disorders</p>

## SPASMODICS

**Action**—Spasmogenic drugs may increase gastrointestinal motility by (1) directly stimulating the muscle cell, (2) stimulating cholinergic activity, and (3) potentiating cholinergic activity. The last is accomplished by preventing a normally-occurring enzyme, cholinesterase, from destroying acetylcholine, the chemical mediator of the parasympathetic system. Drugs of this type exhibit anticholinesterase activity.

**Cholinergic Compounds**—These consist of acetylcholine and its various substitutes. Acetylcholine itself is too unstable to be used clinically, but a more suitable preparation is available in the form of acetyl beta methylcholine chloride (mecholyl). Given parenterally, mecholyl is an active spasmogenic agent, oral administration is less satisfactory because absorption is variable and large doses have to be used to obtain an effect. The stimulation of intestinal motility which follows the injection of mecholyl is usually of short duration but is often quite intense. The patient, for example, may complain of severe abdominal discomfort and cramps. Further discomfort to the patient is produced by marked side reactions which consist of sweating, profuse salivation and general discomfort. Because of these untoward effects and the often violent intestinal contractions, mecholyl is not used extensively as a spasmotic agent. On the other hand, its use has been recommended in such chronic conditions as megacolon, treatment consisting of 100 to 200 mg (grains  $1\frac{1}{2}$  to 3) given orally once or twice a day.<sup>29</sup>

In an attempt to obviate some of the objectionable features of mecholyl, carbaminoylcholine (doryl) and the urethane of beta methylcholine (urecholine) have been synthesized.<sup>30-31</sup> These drugs appear to have a greater action on the genitourinary and gastrointestinal tracts than on the glandular, cardiovascular and respiratory systems. Doryl is a powerful and stable agent, but its very stability renders it a somewhat dangerous drug. Toxic reactions include not only the usual effects of parasympathetic stimulation, but also malaise, nausea, faintness and occasional collapse. Because doryl is so stable, toxic reactions which follow its administration cannot be combated effectively with atropine. In view of the complications that attend the use of doryl, its use as a spasmotic agent is not recommended.

Of the group of acetylcholine substitutes, urecholine appears to offer the greatest promise for clinical use. In spite of a somewhat reduced potency when compared to either mecholyl or doryl, urecholine produces a clear-cut increase in peristalsis and tone. At the same time, cardiovascular effects are minimal. The effect of urecholine becomes ap-

parent within five to twenty minutes of its subcutaneous administration, and within thirty minutes after an oral dose. Its action persists for a period of thirty to sixty minutes. Clinically urecholine has found its greatest use in the treatment of gastric retention following vagotomy for peptic ulcer.<sup>22</sup> The effect of urecholine on the gastrointestinal tract other than the stomach and duodenum is still under investigation. Pending completion of these studies urecholine is not generally available but present indications are that it will prove to be a very useful spasmogenic agent.

*Side Reactions and Toxic Effects*—As noted above the side reactions produced by the acetylcholine substitutes are the results of general parasympathetic stimulation: perspiration, salivation, cardiac slowing, increased activity of uterus and urinary bladder, vasodilatation, fall in blood pressure and bronchoconstriction. If troublesome these side reactions can be counteracted except in the case of doryl with an injection of atropine sulfate 0.6 mg. (grain 1/100) subcutaneously. In general, patients who are known to suffer from asthma should not be given cholinergic drugs.

*Pituitary Extracts*.—Pituitrin and pitressin contain principles which are believed to act directly on the smooth muscles of the gastrointestinal tract and blood vessels. With respect to these pressor principles pitressin is twice as potent as pituitrin. Although the effect of pituitary extracts differs somewhat in various types of animals, an injection of pituitrin or pitressin in man is usually followed by a brief increase in gastrointestinal motility.<sup>23, 24</sup> Since peristaltic waves are stimulated but tone not appreciably affected the net result of an injection of pituitary principles is an increase in propulsive motility; that is, the transport of contents along the enteric canal is promoted. In some cases increased motility has been observed for one hour after injection of pituitrin<sup>25</sup> but usually the response is shorter. Side reactions which express the effect of pituitary extracts on blood vessels consist of pallor, headache and tachycardia.

*Anticholinesterases*.—Physostigmine is a naturally occurring anticholinesterase but it has been replaced in clinical practice by the synthetic product neostigmine (prosgimine) which is more stable, produces less side reactions and is probably more effective as a stimulant of gastrointestinal motility.

Prosgimine has been described by Adler et al.<sup>26</sup> as the best single drug for stimulating the motility of the human colon. Not only is the tone of the intestine increased but propulsive and coordinating waves are enhanced. With the doses required to produce such motor effects no side reactions are noted. A similar increase in the motility of the



small intestine has been noted by us<sup>3</sup> and by Schwab and Chapman<sup>4</sup> after the administration of neostigmine. When given intramuscularly, the effect of prostigmine methylsulfate develops within fifteen to thirty minutes and lasts one hour or longer. The oral preparation, prostigmine bromide, produces a more variable effect which usually starts in thirty to sixty minutes and persists for several hours.

Ergot alkaloids have little effect on gastrointestinal motility and, in large doses, predominantly affect other organs. For these reasons, ergot like substances have no application per se in the treatment of gastrointestinal motor disorders. On the other hand, the action of neostigmine appears to be potentiated by small doses of ergotamine tartrate (gynergen). Thus Adler et al.<sup>23</sup> have found that 0.25 mg (grain 1/240) of neostigmine, when injected with 0.25 mg (grain 1/240) of ergotamine tartrate, exceeds the effect of 0.5 mg of neostigmine. The same authors suggest a combination of spasmogenic drugs consisting of neostigmine and ergotamine in the doses given plus 1.25 units of pitressin. This combination appears logical, for pitressin has a brief and rapid action, neostigmine and ergotamine a more delayed but also a more prolonged effect.

**D F P**—A discussion of the anticholinesterases would be incomplete without mention of D F P or di-isopropylfluorophosphate. Originally investigated as a substance related to chemical warfare, it was found to have marked anticholinesterase activity. It differs from neostigmine in that the inhibition of cholinesterase by neostigmine is temporary and reversible, whereas D F P reduces the enzyme irreversibly for several weeks. Quilliam<sup>27</sup> has employed this drug in doses of 1.5 cc. (minims 22) of a 0.1 per cent solution injected intramuscularly in several cases of postoperative ileus and considers it more effective than prostigmine or pituitary extract. On the other hand, Comroe et al.<sup>28</sup> report that doses of 2 to 3 mg (grain 1/30–1/20) may induce nausea with gastric hypotonicity. Until more information is available, it is not recommended that D F P be used as a spasmogenic agent.

### GENERAL DISCUSSION

The therapeutic use of spasmotics presents, on the whole, less problems than pertain to the use of antispasmodics. In the first place, the clinical conditions that call for spasmogenic substances occur much less frequently than those that indicate antispasmodic therapy. Secondly, the available preparations include a number of agents that are unequivocally effective, produce few side reactions, and yet differ sufficiently in the chronology and character of their action that the physician can choose the drug most suited to his needs. Thus urecholine

offers promise in the treatment of postvagotomy complaints severe constipation and even megacolon often respond very well to the oral administration of prostigmine bromide and ergotamine tartrate and paralytic ileus can be attacked fairly successfully by parenteral injections of pitressin prostigmine and ergotamine. In dealing with paralytic ileus however the efficacy of any spasmogenic treatment is determined to some extent by the degree of intestinal distention. Marked distention particularly if present for a long time often responds poorly to treatment, partly because the extreme stretching of the intestinal muscle may impair its contractile powers and partly because massive distention may interfere with an adequate blood supply. The best treatment of ileus with spasmodics should consequently be anticipatory. Spasmogenic agents should be given if paralytic ileus is feared or is just beginning; once the intestine is fully distended treatment with drugs may prove disappointing. As has been repeatedly emphasized spasmodics are contraindicated if intestinal distention is associated with organic obstruction of the gut or with a localizing peritoneal infection.

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# RECENT ADVANCES IN THE MEDICAL TREATMENT OF ESSENTIAL HYPERTENSION WITH PARTICULAR REFERENCE TO DRUGS

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There is no disease for which specific therapy is more urgently needed than essential hypertension. Statisticians estimate that half of the population over the age of 40 will die of hypertension or its complications and that there are 15,000,000 people with hypertension in the United States today. Results with surgical sympathectomy, and with special diets in the treatment of hypertension have demonstrated that the blood pressure may be lowered in certain patients without harmful effects and, indeed, with apparent benefit. In such cases it seems obvious that elevation of the blood pressure fulfills no necessary function and should be corrected, provided it can be done by benign methods. This paper summarizes the experience in this clinic with the pharmacological treatment of hypertension with particular reference to new hypotensive agents.

## GENERAL CONSIDERATIONS

Not all hypertensive patients require treatment directed at reducing the blood pressure. In mild cases a conservative approach utilizing psychotherapy, sedation, reassurance, and a regimen of living designed to ease the customary tensions of life probably is the treatment of choice. This conclusion is supported by the observation that certain patients, particularly females, may live out a normal life span without treatment of any kind. Nevertheless, statistics derived from large series such as those of insurance companies definitely prove that in general hypertension shortens life. Therefore, a prime consideration in determining therapy for a given patient is to assess his prognosis without treatment.

**Prognostic Signs**—The most significant of the prognostic signs are as follows:

1. *The Level of Blood Pressure*—An elevation of diastolic pressure above 120 mm. of mercury usually indicates a poor prognosis. The level of systolic pressure must be interpreted with certain reservations. For example, elderly individuals whose larger arteries have lost their elasticity may exhibit systolic pressures out of proportion to the diastolic

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levels, whereas young nervous patients under emotional stress may have temporary systolic without diastolic elevations. As a general rule, however, as systolic pressure rises over 200 mm of mercury it warrants a progressively graver prognosis.

2 *The Lability of the Blood Pressure*—Experience has shown that hypertensive patients whose blood pressures fall markedly after a period of rest in bed generally have a more benign form of the disease and respond more readily to conservative medical treatment than patients whose blood pressures are fixed. Similarly, a marked hypotensive response to sodium amytal "narcosis," as a rule, denotes a better prognosis than a slight or negative response to this test.

3 *The Optic Fundi and the Kidneys*—The development of neuroretinitis with papilledema indicates a malignant transition, it is almost always associated with increased levels of diastolic pressure and signs of renal impairment such as the presence of albumin, red cells and/or casts in the urine, impairment of ability to concentrate the urine and excrete phenolsulfonphthalein normally. When these signs develop death occurs usually in less than one year in untreated patients. If the optic fundi are examined frequently the diagnosis of a malignant change may be made before the disease has progressed to an irreversible stage, and life may be prolonged considerably by sympathectomy, dietotherapy, or drug treatment either alone or preferably in combination.

4 *The Cardiac Status*—Enlargement of the heart by physical signs and roentgenography, decreasing exercise tolerance, paroxysmal nocturnal dyspnea, the appearance of an aortic-diastolic murmur, gallop rhythm or pulsus alternans all indicate imminent or obvious cardiac failure. These signs and symptoms may respond to digitalis for a time, but as a rule they require, in addition, rigid sodium restriction and hypotensive drugs.

Such tests as the cold and postural test, the sedation test, renal function tests, examination of the heart and fundi are at best prognostic guides, and also may be of value in selecting patients for surgical sympathectomy. However, these tests are of little use in deciding which type of therapeutic procedure, diet, surgery, or drugs will produce the greatest reduction of blood pressure and relief of symptoms in the individual case. As yet, there are no tests other than a therapeutic trial to determine the most effective hypotensive procedure.

#### CRITERIA FOR EFFECTIVENESS OF HYPOTENSIVE DRUGS

During the past several years in this clinic the effects of a variety of drugs have been investigated in hypertensive patients. In this study the following therapeutic criteria have been used to assess the relative effectiveness of these agents:

1 The first requirement of a therapeutic agent for hypertension is that it should lower the blood pressure significantly in a fair proportion of patients. A host of drugs and nostrums have been used in the past with no proven hypotensive effect in most cases. Controlled studies have demonstrated that such substances as extracts of onion, mistletoe, garlic and watermelon seed, the organic nitrates and the xanthines do not lower the blood pressure significantly in the doses customarily advised.

2 The hypotensive effect should be accomplished without serious detriment to the patient. For example, certain procedures such as the administration of pyrogenic substances, bleeding to the point of collapse or starvation cannot be considered therapeutic even though they lower blood pressure. Likewise certain pharmacological agents such as pentaquine, while effective in lowering blood pressure, are too toxic for clinical use.

3 Accompanying the hypotensive response there should be definite clinical indications of arrest or preferably reversal of the disease, such as symptomatic relief, a reduction in the cardiac size, clearing of neuroretinitis and/or other evidences of general improvement.

4 The drug should have a duration of action of at least eight hours, otherwise the necessity for frequent dosage interferes with the patient's normal habits of life, particularly with his sleep. Examples of drugs whose duration of action is too brief to be of value in long term treatment are sodium nitrite and tetraethylammonium salts.

5 Finally a satisfactory agent should be effective by mouth or at least by subcutaneous injection. An agent such as dibenamine that must be administered in a dilute solution by slow intravenous drip is not practical for long term treatment.

With these criteria in mind it seems worthwhile to review the more useful of the medical procedures that have been applied in the treatment of essential hypertension.

#### POTASSIUM THIOCYANATE

The therapeutic effectiveness of the thiocyanates in essential hypertension has been a controversial point. Experience in this clinic has demonstrated a significant reduction of blood pressure in somewhat less than 10 per cent of patients treated. In these few cases, however, the response has been quite favorable with freedom from toxic effects and relief of symptoms. In some patients there has been relief of symptoms, particularly headache and emotional irritability, without a demonstrable lowering of blood pressure, while in others there has been aggravation of symptoms.



As a result of these experiences the use of thiocyanate in this clinic is now restricted to the few patients who after a trial period of several months have exhibited a definite hypotensive effect. If the blood pressure is not significantly reduced after such a trial the drug is withdrawn and some other form of treatment substituted. Before beginning treatment it is important to evaluate the efficiency of the kidneys by means of the history and such laboratory procedures as the routine urinalysis, the concentration-dilution test, the phenolsulfonplithalein test and the blood nonprotein nitrogen concentration, since patients with renal impairment may develop high serum levels of thiocyanate on relatively low dosage.

Because the thiocyanates are potentially highly toxic substances when the level in the blood exceeds 10 to 12 mg. per 100 cc. it is imperative that the physician using this agent have at his disposal some means of making frequent determinations of the blood thiocyanate concentration. It is well also to keep in mind the type of toxic reactions that may be encountered, since fatalities have occurred with careless administration.

The severe reactions are psychosis and exfoliative dermatitis. Severe toxic psychosis is the most dangerous of the toxic symptoms as it precedes the majority of deaths. The clinical state may be characterized by dysarthria, mental dullness, aphasia, delirium, clonic contractures and hallucinations. In fatal cases, despite discontinuation of the drug, there is a progressive downhill course with stupor, convulsions, sphincter incontinence, collapse and death. The majority of such fatalities have occurred in patients whose blood levels were not carefully controlled.

Less severe toxic manifestations such as gastrointestinal disorders including diarrhea, nausea and vomiting, and abdominal pain are seldom observed unless the blood level rises above 12 mg. per 100 cc. Various types of dermatitis including exanthematous, acneiform, or iodotic rash, furunculosis and purpura may occur but disappear soon after discontinuation of treatment.

Thyroid enlargement, mild myxedema and even goitre may appear during thiocyanate administration, an effect produced by thiocyanate blockade of the formation of thyroxin in the thyroid gland. The block may be overcome by administration of an excess of iodine in the form of a saturated solution of potassium iodide (10 drops three times per day in water). General weakness and fatigue occurs in more than half the cases but tends to disappear after several weeks or months of continued treatment.

Treatment with potassium thiocyanate is begun by the administra-

tion of 0.06 gm (1 grain) in enteric coated tablets \* three times per day before or after meals. The blood level must be determined at least once each week and is used as a guide in adjusting dosage. Dosage is increased by 0.06 to 0.12 gm (1 to 2 grains) at weekly intervals until the serum concentration reaches 8 to 12 mg per 100 cc and is maintained at this level for at least three weeks, with weekly checks of the blood pressure and serum concentration of thiocyanate.

If no hypotensive response occurs at the end of three to four weeks the drug is withdrawn. However, if there is a definite reduction in blood pressure or marked symptomatic improvement dosage is gradually adjusted downward. The reason for thus reducing the dosage is that many patients who respond to thiocyanates will have as good a therapeutic effect and not as much toxicity with blood levels between 4 and 8 mg per 100 cc, as they will with levels between 8 and 12 mg per 100 cc. After final adjustment of dosage the patient may be seen at intervals of approximately one month when the blood levels always should be determined.

It is impossible to predict the dosage required by any patient from his surface area or other available criteria; the dose required to maintain a therapeutic blood level varies from 0.2 to 0.6 gm of potassium thiocyanate daily. Therefore, under no circumstances may thiocyanate be administered unless there are laboratory facilities available for determining the serum levels of the drug.

### SYMPATHOLYTIC AGENTS

Surgical sympathectomy in the treatment of essential hypertension has stimulated great interest in chemical agents which will block sympathetically innervated vasoconstriction. Several blocking agents have been produced but for various reasons few of these are practical in the long term clinical treatment of patients.

Examples of sympatholytic agents studied in hypertensive patients in this clinic are tetraethylammonium salts, dibenamine, pentaquine and the dihydrogenated derivatives of ergotoxine. These agents have certain pharmacologic effects in common: they all may produce a fall of blood pressure, particularly in the erect position, but the duration and the degree of the fall are extremely variable in different patients and are not related directly either to dosage or to the completeness of sympathetic blockade. Other evidences of sympatholysis, including nasal stuffiness, inhibition of reflex sympathetic vasoconstriction in the fingers and toes, and depression of vasopressor responses may also vary greatly in different patients.

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\* Supplied by the Eli Lilly Company

The duration of the sympatholytic action varies with the drug used, tetraethylammonium being the shortest, the dihydrogenated derivatives and dibenamine intermediate, and pentaquine the longest acting. Pharmacologically these drugs are of interest because they block the sympathetic nervous system at different sites.

*Tetraethylammonium bromide or chloride* (Etamon\*) is effective only by parenteral administration. The dose of Etamon administered intravenously is 0.2 to 0.3 gm. Although the drug has been used therapeutically in peripheral vascular disease, especially in angiospastic conditions of the extremities such as Raynaud's disease and thromboangitis obliterans, the duration of the hypotensive response is too brief to be of value in treating hypertensive patients. Further, because there is also parasympathetic blockade, the hypotensive response is accompanied by tachycardia and palpitation, particularly in the erect position. There is usually some paralysis of visual accommodation.

*Dibenamine* (dibenzyl-bis chloro ethyl-amine) is said to block sympathetic impulses peripherally at the effector cells. Being a nitrogen mustard derivative it is too caustic to be administered by any other route than intravenously in dilute solution by constant slow drip. The dose of 5 mg. per kg. is diluted in 500 cc. of saline administered over a period of an hour. Despite meticulous technic patients may develop chemical thromboses at the sites of administration. In animals the drug blocks or inhibits both excitatory sympathetic nervous functions and the effects of epinephrine. In man in therapeutic doses an adrenolytic effect has seldom been observed, but its sympatholytic effects, including hypotension, may last from several hours to several days. Visual accommodation is impaired and in some female patients we have noted temporary loss of voluntary bladder control in the erect position.

*Pentaquine*, a synthetic derivative of plasmochin, was developed during the war for the treatment of malaria. It was noted that when the drug was administered to both normal individuals and malarial patients postural hypotension occasionally developed and persisted for several weeks or longer. In animals it was found that both pentaquine and plasmochin block sympathetic reflexes in the central nervous system rather than at the ganglia or peripherally. In hypertensive patients, including those in the malignant phase of essential hypertension, there was a variable but often striking reduction of blood pressure after several days of oral administration. Such large doses were required that many patients developed toxic effects including abdominal pains, weakness, anorexia and methemoglobinemia. Visual accommodation was not

impaired. The postural hypotension which lasted several days to several weeks following discontinuation of the drug differed from that observed with tetraethylammonium and dibenamine in that it was not accompanied by significant increase in pulse rate. Several patients with advanced malignant hypertension were treated and it is significant that despite continued hypotension their nitrogen retention gradually increased and they eventually died in uremia.

The *dihydrogenated alkaloids of the ergotoxine group* like pentaquine are believed to produce a central blockade of sympathetic reflexes. To date the most useful hypotensive agent in this group of three compounds has been dihydroergocornine (DHO 180). It was effective by any route, the intravenous dose being approximately 0.25 mg and the oral dose 2 to 8 mg administered prior to breakfast. In reactive patients the hypotensive effect lasted eight hours to several days. The drug was remarkably free of toxic side effects particularly when administered orally. Transient nasal stuffiness was the only side effect noted following oral administration.

Postural collapse from DHO 180 could be avoided in most patients by reducing the dosage or by fitting the patient with an abdominal binder and elastic stockings. Nausea and vomiting occurred occasionally after intravenous administration. Although supplies of this agent are still limited to investigational work it would appear at present to be the most promising of the sympatholytic agents for use in treating hypertensive patients. However, final evaluation of this drug must await further clinical studies.

It is by no means certain that any sympatholytic drug will provide a solution to the problem of treating the majority of hypertensive patients. Unfortunately not all patients react to these drugs with a fall in blood pressure. Despite complete abolition of sympathetic vasomotor reflexes some patients fail to exhibit significant hypotension suggesting that in these individuals mechanisms other than an overactive sympathetic nervous system are involved in maintaining the hypertension. Further, the sympatholytic agents that act peripherally produce disturbances in visual accommodation while all of them cause postural hypotension and moderate debility as concerns sudden physical effort. Finally this whole approach to the problem of hypertension is so recent that little should be concluded as to its ultimate value.

#### VERATRUM VIRIDE

Of all the drugs used in this clinic to lower blood pressure in essential hypertension *veratrum viride* has produced the most marked reduction of blood pressure in the greatest number of patients. Recent

studies of its clinical and pharmacological effects indicate that the hypotensive action may occur in subtoxic dosage, and that there are no harmful effects on the heart or kidneys following acute or chronic administration.

The veratrum alkaloids have been condemned in pharmacologic textbooks because they were thought to be cardiac depressants, and because they were misused in the past to "soften the pulse" and lower the body temperature in febrile illnesses. However, more recent pharmacologic investigations in animals and in hypertensive patients have demonstrated that the fall in blood pressure which occurs after therapeutic doses of the drug is due to a decrease in peripheral resistance rather than to a depression of cardiac output. As the blood pressure falls the blood flow through the liver, the kidney and the extremities at first decreases slightly, but then returns to or even above the previous levels despite a continued reduction of blood pressure. From animal experiments it is known that the veratrum alkaloids stimulate the afferent vagal nerve endings in the thorax and particularly in the myocardium of the left ventricle from which nervous discharges travel to the brain and initiate a reflex fall in blood pressure and usually in pulse rate. The slowing of cardiac rate presumably is due to stimulation of the efferent vagus because it may be abolished by atropine, but the other efferent pathways which cause the hypotension are not known. Studies have shown that the sympathetic reflexes are not blocked and that the cholinergic vasodilator nerves are probably not stimulated since atropine does not abolish the hypotension.

Clinically veratrum viride may be administered parenterally (Veratrone\*) or orally (Vertavis†). The oral preparation seems preferable because it is more readily administered and its hypotensive effect is of longer duration. Vertavis tablets contain the whole dry powdered veratrum viride biologically standardized so that each tablet contains 10 Craw units. Following an effective oral dose of the drug the hypotensive effect usually begins in one to two hours, reaches a maximum in four to six hours, and ends in ten to fourteen hours. Therefore, in order to avoid cumulative overdosage it is usually expedient to administer the drug at eight to twelve hour intervals.

Successful treatment with veratrum requires meticulous attention to dosage because of the nausea and vomiting that may occur, particularly during long-term administration. These undesirable side effects may appear with doses only slightly greater than the therapeutic dose, and in some patients with doses insufficient to produce a hypotensive effect.

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\* Parke Davis and Company

† Irwin, Neisler and Company

However in most patients successful therapeutic results can be achieved by proper spacing of dosage.

There is a great variability from patient to patient in the amount of veratrum required to produce a hypotensive response. Therefore, in hospitalized patients the effective dose must be determined in each instance by administering one tablet of Vertavis (10 Crawl units) every two hours until a therapeutic or toxic effect results. Having found the level to which the patient responds this dose is administered at twelve hour intervals morning and night. Vomiting is less often encountered if each twelve hour dosage period is further subdivided so that no more than 10 Crawl units are administered each hour.

In ambulatory patients dosage is begun by instructing the patient to take one tablet (10 Crawl units) before breakfast and before the evening meal. The patient is seen the next week approximately four to six hours after the morning dose and his blood pressure is taken. If no hypotensive effect is observed and there have been no toxic reactions, the dose is increased to 10 Crawl units before breakfast and one hour later after breakfast before supper and one hour later after supper (four tablets per day). In this way the amount of the drug is increased by one or two tablets a day at weekly intervals until the effective and/or toxic dose has been determined. Occasionally patients may require readjustment of dosage either upward or downward after weeks or months of continuous treatment.

The hypotensive response to long-continued administration is seldom as dramatic as that seen after short term administration. For this reason results have been especially favorable in the treatment of hypertensive encephalopathy when the drug was administered in doses of 10 Crawl units every hour or two until the blood pressure was reduced. However long-continued treatment resulted in a significant reduction of blood pressure in about one third of the patients treated when dosage was carefully readjusted as the need arose. The hypotensive response was usually accompanied by symptomatic relief of exertional dyspnea, palpitation, nervous irritability and headache. Attacks of angina pectoris in some cases became less frequent but in others did not change. More objective signs of improvement were evidenced by a diminution in cardiac size, occasional reversal of the left ventricular strain patterns in the electrocardiogram and clearing of hemorrhages and exudates in the optic fundi. Pulenis manifesting albuminuria and a decreased excretion of phenolsulfonphthalein continued to exhibit these signs of renal impairment despite other evidences of improvement. Thus, clinically improvement was evidenced in the heart and optic fundi but not in the previously damaged kidneys.

As already mentioned the principal side effect of *veratrum viride* was the development of nausea and vomiting, often accompanied by a sense of tightness in the throat, excessive salivation and occasionally by paresthesias about the mouth, jaw, hands and feet. Rarely there was a transient blurring of vision which was apparently unrelated to paralysis of visual accommodation. All these effects disappeared within a few hours after discontinuing the drug.

If too large a dose was given at one time or if doses were given at too frequent intervals a cumulative effect occurred, with a profound reduction in blood pressure, and collapse in the upright position associated with severe vomiting and marked bradycardia. The bradycardia and to some extent the vomiting could be abolished by doses of 1 mg (1/60th grain) of atropine intravenously or intramuscularly and the hypotension by ephedrine (0.05 gm intramuscularly). Such marked hypotension and bradycardia, which conceivably might predispose toward cerebral or coronary artery thrombosis, especially in arteriosclerotic patients, should be avoided by careful attention to the methods of adjusting dosage outlined above.

About 10 to 20 per cent of the patients failed to exhibit a hypotensive response to subtoxic doses of *veratrum viride* and in these patients treatment with this drug had to be abandoned. In another small percentage the addition of half the morning or evening dose at 2:00 P.M. was necessary to continue the hypotension because the hypotensive effect was maintained for no more than six hours following administration of the drug. It is evident, therefore, that because of two factors, the great variability of the effective dose in different patients, and the narrow margin between the therapeutic and toxic doses, treatment with this agent requires considerable attention and persistence on the part of the physician.

#### DIETOTHERAPY

Although this paper is concerned primarily with drug therapy, recent advances in dietotherapy merit additional comment. The Kempner rice diet has been difficult to administer in this clinic over long periods principally because of the unpalatability and monotony of the diet and also because of the weight loss and weakness encountered in some patients. Further, experience so far fails to indicate that the rice diet provides a greater reduction in blood pressure or more symptomatic relief than a salt free diet as advocated by Allen many years ago.

Most of the so-called "salt free" diets advocated in the past have not provided sufficient restriction of sodium. The sodium content of the daily ration should be reduced to below 0.5 gm. for satisfactory results.

The preparation of such diets may be aided by substituting salt free milk powder (Lanolinac \*) and salt free bread. The Mead Johnson Company recently have conducted sodium analyses of commonly used American foodstuffs. A list of the sodium content of these foods and the menus of diets poor in sodium may be obtained from the research department of this company. The flat taste of food prepared without salt may be counteracted to some extent by the use of a salt substitute the principle ingredient of which is potassium chloride (Neocurtasal †). In addition since there is no evidence that caffeine aggravates hypertension patients are allowed to flavor the salt free milk powder with coffee tea or cocoa. Meat and fresh fish in small amounts and almost all vegetables are permitted. These modifications permit a palatable varied and nutritious diet which is sufficiently low in sodium content. Additional salt deprivation may be obtained by administering a mercurial diuretic once or twice per week.

Approximately half of the patients maintained on either the Kempner rice diet or the salt poor diet manifested a significant reduction in blood pressure after several weeks. All patients with hypertension complicated by cardiac failure are benefited by sodium restriction and mercurial diuretics regardless of any hypotensive effect. Certain patients with far advanced hypertensive disease and renal failure responded poorly probably because of the excessive amounts of sodium which these patients customarily lose in the urine. In such patients it is possible to produce collapse and increased nitrogen retention through strict restriction of sodium.

### COMBINED THERAPY

Drugs and dietotherapy in combination often may be used to advantage. Thus, patients who exhibit only slight to moderate hypotensive responses with either adequate salt restriction or veratrum viride alone may be definitely benefited by the combination of both types of treatment. Likewise either or both treatments may be more effective after as compared with before lumbodorsal splanchnicectomy. Similarly, dihydroergocornine in reactive patients has enhanced the hypotensive effects of either the salt poor diet or veratrum or both.

In addition to these more or less specific measures the treatment of the personality of the patient in relation to his environment plays an important part in the well managed case. A sympathetic and hopeful attitude, the willingness to listen to the patient's personal problems

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\* Mead Johnson Company

† Winthrop



the prescribing of rest periods and the wise use of occupational therapy provide additional supports to a well rounded plan of therapy

In conclusion, it is apparent that as yet no single method of treatment will produce a satisfactory reduction of blood pressure in every patient with essential hypertension. However, the recent additions of sympathectomy, dietotherapy and effective hypotensive drugs such as veratrum viride and dihydroergotornine to our armamentarium has provided the beginnings of a more positive therapeutic approach to the disease. The ultimate value of these newer therapeutic procedures must await the test of time.

## THE TREATMENT OF ANEMIA

CHARLES P. EMERSON, JR., M.D.\*

Adequate therapy in cases with anemia necessarily implies the fundamental assumption that a reduction of the blood hemoglobin concentration is not a disease *sui generis* but invariably a complication of some underlying disorder the identification of which in each case is essential to its appropriate management. Patients with a wide variety of unrelated diseases and with vastly different therapeutic requirements may exhibit this sign as the most prominent clinical feature of their illness. Its appearance as an outstanding manifestation in cases of pernicious anemia or following acute hemorrhage is naturally to be expected that it frequently is the sole source of presenting symptoms in patients with unrecognized chronic blood loss with insidious neoplastic diseases invading the bone marrow and with toxic drug reactions is a fact that may be overlooked.

Antianemic therapy conducted purely on an empiric basis without regard to the etiologic background can no more be justified than the symptomatic treatment of unexplained abdominal pain directed exclusively for the relief of discomfort. Thus if the maximum number of anemic patients are to receive optimal care and the risks of therapeutic neglect are to be reduced to a minimum a critical diagnostic appraisal must be accepted as a necessary preliminary to treatment. Attempts to elucidate fully the etiologic factors operative in each case of anemia can not be classed merely as an academic pursuit, or of value chiefly as a means of avoiding economic waste in therapy. The ideal objective is to cure the underlying disease or defect, whenever possible otherwise to provide adequate compensatory measures for the alleviation of its effects, not only on the blood, but on every organ system potentially involved. Attainment of these objectives clearly depends upon the establishment of an accurate diagnosis on the basis of which a logical therapeutic program can usually be devised and an optimal response predicted.

### THE DIAGNOSTIC APPROACH

A specific etiologic diagnosis can be determined in the majority of cases of anemia on the basis of data available from a comprehensive

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clinical examination and an appropriate, relatively simple, laboratory investigation

**The Clinical History**—The patient's personal and family histories often contribute information that is indispensable for diagnosis. Specific inquiry should be made with respect to the following

- 1 Character of the onset of symptoms conceivably attributable to anemia, including pallor, increased fatigability, exertional dyspnea or anginal attacks.
- 2 Symptoms consistent with acute hemorrhage or chronic blood loss in the recent or remote past
- 3 Symptoms of diseases commonly complicated by hemorrhage.
- 4 Possible evidences of purpura or of spontaneous bleeding
- 5 History of acute or chronic jaundice, and unusual coloration of urine or feces
- 6 Familial incidence of anemia, jaundice, or hemorrhagic disorders
- 7 History of exposure to toxic chemical agents, and of chemotherapy received
- 8 History of dietary restrictions, and gastrointestinal disorders
- 9 Symptoms of neurologic dysfunction, including dysesthesias, ataxia and muscle weakness
- 10 History of febrile illnesses
- 11 Symptoms consistent with renal disease

**Physical Signs**—The presence or absence of certain abnormal findings must routinely be established. *Icterus* suggests the possibility of a hemolytic disorder, hepatic disease or both, in the *absence of icterus*, an acute hemolytic process is unlikely. Massive *splenomegaly* and chronic progressive *lymph node enlargement* usually denote a malignant neoplasia, e.g., one of the leukemias or lymphomas, the total *absence of splenomegaly* may be regarded as valid evidence for the exclusion of many diagnoses, among which are congenital hemolytic jaundice, thalassemia major (Cooley's anemia), certain acquired hemolytic disorders, chronic malaria, generalized bacterial sepsis and portal hypertension. Even greater diagnostic specificity attaches to signs of combined system disease in pernicious anemia, the presence of friable, flat, or spoon shaped fingernails in association with chronic iron deficiency, of spider angiomas in hepatic cirrhosis, and the telangiectatic lesions characterizing congenital hemorrhagic telangiectasia.

**Laboratory Study**—A precise etiologic diagnosis can seldom be established without the support of data indicating the rapidity of blood production and blood destruction and the character of erythropoiesis, as well as the presence or absence of hemorrhagic, infectious and renal disease.

The erythropoietic rate can be estimated from the number of reticulocytes in the peripheral blood, normally ranging from approximately 15 000 to 50 000 per cubic millimeter. A substantial increase in the reticulocyte count indicates an enhanced rate of red cell production and occurs as a normal response to anemia. When reticulocytosis is of marked degree precipitated for example by a massive hemorrhage or an acute hemolytic process nucleated red cells normally retained in the bone marrow may appear in the peripheral blood.

Evidence indicating the rate of blood destruction may be adduced in part from the concentration of plasma bilirubin (normally less than 1 mg per 100 cc.) or the icterus index (usually not exceeding 7 units) and partially from the estimated rate of blood production. The coexistence of icterus and reticulocytosis usually denotes a hemolytic process.

Abnormalities in the character of red cell maturation are reflected by alterations in red cell morphology detectable on inspection of the stained blood film. The presence of abnormally large or small erythrocytes, excessive variation in their size or shape and the appearance of stippled cells, are indicative of faulty erythropoiesis. Quantitative data with respect to the size and hemoglobin content of the red cells are particularly informative and should be obtained in every case of obscure anemia. Indices to be determined<sup>1</sup> include the estimated average red cell size or mean corpuscular volume (MCV) normally between 82 and 93 cubic microns; it is calculated as follows:

$$MCV = \frac{\text{volume of packed red cells per 1000 cc. whole blood}}{R.B.C. \text{ (millions per cu. mm)}}$$

Macrocytosis implies a significant increase and microcytosis a definite reduction in the mean corpuscular volume.

The hemoglobin content of the average cell or the mean corpuscular hemoglobin (MCH) normally 27 to 31 micrograms is determined from the total blood hemoglobin concentration and the red cell count.

$$MCH = \frac{\text{Hgb (gm per 1000 cc of blood)}}{R.B.C. \text{ (millions per cu. mm)}}$$

The concentration of intracorpuseular hemoglobin or mean corpuscular hemoglobin concentration (MCHC) is derived from the total hemoglobin concentration and the hematocrit reading. Expressed in terms of percentage the normal values are between 32 and 36.

$$MCHC = \frac{\text{Hgb (gm per 100 cc)}}{\text{vol of packed red cells (cc. per 100 cc)}}$$

If the MCHC is found to be appreciably less than 32 per cent, the blood picture is described as hypochromic

### PROBLEMS OF CLASSIFICATION

A systematic classification of disorders complicated by anemia is indispensable as a diagnostic guide. One method of cataloguing these diseases, especially useful because of its therapeutic implications, is based on the morphologic characteristics of the red cells. Alterations in the average size and hemoglobin content of the erythrocyte alone provide presumptive etiologic evidence in the most prevalent types of anemia, as screening tests for limiting the diagnostic possibilities, such data are indispensable. Unfortunately, however, certain anemic states are not regularly manifested by hematologic changes of peculiar significance, and hence cannot logically be categorized solely on a morphologic basis. Furthermore, except for the sickling phenomenon in sickle cell anemia and the presence of parasitized cells in malaria, there is no single morphologic characteristic that may not be shared by a variety of diseases attaching altogether different prognoses and therapeutic indications. Thus, the same degree of macrocytosis may denote pernicious anemia, chronic liver disease, one of several nutritional disorders, or a hemolytic syndrome. Microcytosis and hypochromia provide valid evidence of iron deficiency, usually on the basis of chronic uncompensated blood loss, however, similar changes may result from a disturbance of iron metabolism related to infection,<sup>2</sup> and they are equally characteristic of thalassemia. (Cooley's anemia)

A more logical classification would be one arranged according to pathogenetic mechanisms responsible for anemia, namely, uncompensated blood loss, excessive blood destruction and inadequate blood production. But in some diseases the mechanism of anemia is not altogether clear, nor is it always evident from the available clinical data, in some instances, more than one mechanism may be implicated.

A useful system of classification must be relatively simple, yet involve a minimum of unwarranted assumptions, and should serve to recall the more pertinent aspects of diagnosis and therapy. In the arrangement illustrated below the anemias are grouped according to etiologic diagnoses, and the separate disease entities classified either on the basis of morphologic changes or according to the mode of pathogenesis, whichever device seems more appropriate in the light of present knowledge.

### CLASSIFICATION OF THE ANEMIAS AS A BASIS FOR DIAGNOSIS AND TREATMENT

- I Deficiency states accompanied by inadequate and defective red cell production

- (a) Hypochromic microcytic type due to iron deficiency iron depletion due to hemorrhage or inadequacy of iron intake relative to increased requirements in association with growth and pregnancy
- (b) Macrocytic type due to E.M.F.\* deficiency manifested in pernicious anemia and the macrocytic anemias of pregnancy sprue other steatorrheas dietary deficiency states hepatic cirrhosis gastric malignancy postgastrectomy cases and tapeworm infestation

## II Toxic reactions to chemical agents

- (a) Hemolytic type from damage to circulating red cells agents invariably or potentially hemolytic include phenylhydrazine arsine hydroquinone quinine<sup>2</sup> and sulfonamide drugs.<sup>4</sup>
- (b) Aplastic type with depression of erythrocytic granulocytic and platelet production in the marrow caused by benzol quinacrine<sup>2</sup> uridione<sup>7</sup> compounds of lead arsenic and gold and exposure to ionizing radiation

## III Hemolytic disorders attributable to the damaging effect of red cell antibodies passively acquired or produced by a damaging immune mechanism

- (a) Hemolytic disease of the newborn (erythroblastosis fetalis) due to transplacental absorption of maternal anti Rh isoantibodies from plasma of sensitized mother
- (b) Hemolytic response to therapeutic administration of plasma containing incompatible anti A or anti B isoantibodies.<sup>8</sup>
- (c) Hemolytic jaundice of acquired type with red cell antibodies present in the circulating plasma or absorbed on red cells<sup>9</sup> as demonstrated by the Coombs test<sup>10</sup> with anti human globulin serum
- (d) Paroxysmal hemoglobinuria complicating late syphilis, in which cold hemolysins are demonstrable by the Donath Landsteiner test<sup>11</sup>
- (e) Paroxysmal nocturnal hemoglobinuria in which there may be a hemolytic antibody absorbed on the red cell demonstrable by the acid hemolysis test of Ham.<sup>12</sup>

## IV Hereditary defects of the red cells, responsible for chronic hemolytic disorders

- (a) Congenital hemolytic jaundice: spherocytic red cells manifesting abnormally increased osmotic and mechanical fragility
- (b) Thalassemia major (Cooley's anemia) persistent hypochromia and microcytosis uninfluenced by iron therapy
- (c) Sickle cell anemia with increased blood viscosity due to characteristic morphologic changes in red cells exposed to low oxygen tensions

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\*Erythrocytic maturation factor: the active principle in liver extracts therapeutically effective in pernicious anemia

- V Systemic diseases reducing red cell formation as a result of
- (a) Bone marrow destruction by neoplastic invasion (e g, leukemias, lymphomas, myeloma), inflammatory lesions (e g disseminated tuberculosis) and lipoid infiltrations (e g, Gaucher's disease)
  - (b) Metabolic defects suppressing erythropoiesis, related to infection, renal insufficiency and hypothyroidism

#### TREATMENT OF IRON DEFICIENCY ANEMIA

Unless complicated by continued blood loss or by active infection, this deficiency state, with its attendant hypochromic anemia, readily responds to the ingestion of iron. The latter may be appropriately supplied in a variety of forms, but it is essential that its dosage be ample and its administration sufficiently prolonged. Iron salts that have been widely employed include ferrous sulfate, the optimum daily dosage of which is at least 1 gm daily, ferrous carbonate (Blaud's pills), 4 gm, ferric ammonium citrate, 6 gm, ferrous gluconate, 15 gm, and reduced iron, 3 gm. No iron preparation has proved superior to ferrous sulfate, with respect either to economy or efficacy. Therapeutic response is evidenced, within ten days, by an increase in reticulocyte percentage (rarely exceeding 20 per cent) and a subsequent rise in hemoglobin concentration (0.1 to 0.3 gm per 100 cc per day) until normal values are approached.

The relative toxicity of the several preparations available is extraordinarily difficult to evaluate. All soluble iron salts, in sufficient concentration, exert an irritant effect on the gastrointestinal tract producing abdominal cramps, nausea and diarrhea, a small proportion of patients are thus affected on receiving iron in almost any form if supplied in therapeutically effective doses. This undesirable complication of treatment is largely eliminated by proper scheduling of therapy, insisting that each dose be taken promptly after a meal.

No therapeutic advantage is gained by supplementing iron with other inorganic elements or nutrient materials.<sup>13</sup> Although a variety of supplements are included in most of the iron preparations supplied commercially as "hemopoietic stimulants," there is no proof that these facilitate the absorption,<sup>14</sup> enhance the utilization, or otherwise increase the effectiveness of iron in the treatment of iron deficiency. It is appropriate to emphasize, however, that although one isolated feature may dominate the clinical picture, in most deficiency syndromes more than one element requires replacement. Thus, a well balanced nutritious diet should routinely be prescribed and assured as part of the therapeutic program in treating iron deficiency.<sup>15</sup>

Parenteral iron therapy is rarely necessary. If the oral route cannot,

for any reason be employed or if there exists some gastrointestinal defect impeding the absorption of iron this material may be supplied most effectively and conveniently in the form of whole blood or red cell transfusions

#### TREATMENT OF THE MACROCYTIC ANEMIAS

All macrocytic anemias may be attributed to a common deficiency of erythrocyte maturation factor (E M F) which is supplied in liver extract and as first established by Castle is normally produced by the interaction of a gastric (intrinsic) factor and a dietary (extrinsic) factor E M F deficiency resulting in defective erythropoiesis and macrocytic anemia occurs in pernicious anemia as a result of a deficient production of the intrinsic factor related to some constitutional defect manifested by atrophy of the gastric mucosa Similarly in patients with gastric malignancy and following gastric resection E.M.F. deficiency may develop through failure of intrinsic factor production E.M.F. deficiency may also arise as a result of a deficiency of extrinsic factor on the basis of a grossly inadequate diet or from impaired intestinal absorption of the interaction product as in cases with chronic gastrointestinal obstruction or diarrheal disorders such as sprue coeliac disease and idiopathic steatorrhea In severe liver disease the utilization of this interaction product may be prevented through a fault in metabolism in pernicious anemia of pregnancy a combination of factors are probably involved including the fetal requirements for E M F and a reduced production of intrinsic factor

**Pteroylglutamic Acid (Folic Acid)**—The precise role of pteroyl glutamic acid (PGA) in relation to the normal and abnormal physiology of blood formation as well as its relationship to the liver principle remains to be established This substance in the form of various conjugates is a component of the vitamin B complex present in relatively high concentration in yeast and liver substance. Administered orally or parenterally not as a conjugate but in its free unconjugated form it regularly induces a hemopoietic response in patients with macrocytic anemia comparable to that obtained with parenterally administered liver extract.<sup>26</sup>

Evidence is available<sup>27-29</sup> suggesting that the phenomenon of macrocytosis may in all instances, be attributable to a deficiency of the free vitamin the liberation of which from its bound conjugated form depends on the activity of specific tissue enzymes or conjugases Foods that contain the bound vitamin also contain substances that tend to inhibit this enzymatic activity It is possible that the prime function of the intrinsic gastric factor may be to inactivate these conjugase in



hibitors, thereby permitting the liberation of PGA in its free, effective form by gastrointestinal enzymes.

### TREATMENT OF PERNICIOUS ANEMIA

Anemia, in this disease, is invariably macrocytic in type unless there is an associated iron deficiency. Accompanying signs of gastric achylia, glossitis, evidences of combined system disease, and the findings of moderate granulopenia, thrombopenia and icterus, are of specific value in establishing the diagnosis, the accuracy of which, in view of its therapeutic implications, is unusually important. Restoration of normal health is possible in almost all cases if appropriate treatment is started sufficiently early in the course of the disease, but maintenance of normal health, in contrast to other types of anemia, depends upon the life-long continuation of specific replacement therapy, the only security against the development of incapacitating, and irreversible, neurologic lesions. The diagnosis of pernicious anemia, once a complete therapeutic remission has been obtained, is difficult to prove or disprove, since the only residual characteristic abnormality may be histamine-fast achlorhydria. Every effort should therefore be made to establish the diagnosis on the basis of incontrovertible data, while these are obtainable, to eliminate any possible future doubt regarding the necessity for continued treatment.

Liver extract, administered parenterally at regular intervals, remains the treatment of choice in pernicious anemia. Purified extracts, providing 15 to 20 USP units per cc are completely effective, no merit whatever attaches to the use of less refined extracts, or vitamin supplements<sup>19</sup> including folic acid,<sup>20-24</sup> regardless of the presence or absence of neurologic complications. Adequacy of dosage, as well as regularity of treatment, is extremely important if an optimal sustained remission is to be assured. No toxic symptoms result from excessive doses of liver extract. Therefore, since there is considerable variation in the therapeutic requirements, even in the same patient at different times, it seems wise to administer the drug in a dosage that assures an ample margin of safety. A satisfactory routine, recommended by Haden,<sup>25</sup> imposes the following schedule of parenteral liver therapy.

Patients with pernicious anemia in relapse, without signs of neurologic complications, receive 15 units of liver extract daily for two weeks, 15 units twice weekly for three months, 15 units weekly for three months, 15 units semimonthly for six months, and 15 units monthly thereafter.

Patients exhibiting neurologic complications receive 15 units of liver extract daily for two weeks, biweekly for three months, and

weekly thereafter until it is evident that further improvement will not be obtained, at which time the dosage may be reduced to 15 units semimonthly or monthly

**Response to Therapy**—Within forty-eight hours following the initial dose of liver extract the patient characteristically experiences marked symptomatic improvement with restoration of appetite vigor and sense of well being. Concomitantly the skin may acquire a moderately flushed appearance, and the extremities become relatively warmer. The hematologic response follows a stereotyped pattern sufficiently characteristic of pernicious anemia as to provide complete diagnostic confirmation indeed if the typical response fails to occur the original diagnosis may be questioned. After a three to five day interval, during which time there may occur a slight drop in the red cell count, a reticulocyte response becomes evident the peak concentration of reticulocytes usually appearing between the seventh and tenth days of treatment. This peak value is entirely dependent on the degree of anemia and bears a fairly constant inverse relationship to the original red cell count<sup>20</sup> as follows

<i>RBC before treatment (<math>\times 10^9</math>)</i>	<i>Peak reticulocyte count (per cent)</i>
0.5-1.0	60-40
1.5-2.0	30-20
2.5-3.0	15-10
3.5 and over	less than 5

An increase in red cell count occurs at a rate of approximately 80 000 to 100 000 per day again depending on the initial severity of anemia. Within eight to ten weeks a complete hematologic remission should be attained. Signs and symptoms of combined system disease if minimal or only moderately severe, may be completely relieved and even in severe cases progression of the neurologic lesion is not observed after the initiation of adequate liver therapy.

**Other Therapeutic Considerations**—Inhibition of the typical therapeutic remission may result from the presence of a complicating infection which must be sought and eradicated. Suboptimal remissions may also be attributable to advanced arteriosclerosis in which event more intensive therapy is indicated.

Patients in severe relapse with profound anemia and with evidences of circulatory failure on bed rest or with a complicating infection should promptly receive in addition to liver extract one or two blood transfusions administered cautiously and preferably in the form of red cell concentrates. In all severely anemic cases strict bed rest should be imposed until the red cell concentration has attained a level of approximately two million per cu. mm.

No specific dietary recommendations are routinely necessary in the care of patients with pernicious anemia, except to insure an adequate protein intake. The use of oral preparations containing liver, liver extract, or desiccated gastric mucosa, is generally unnecessary and never required as a supplement to parenteral liver therapy.

Folic acid, administered alone, has proved therapeutically ineffective, with respect to the control or prevention of combined system disease in many cases of pernicious anemia.<sup>21 22 24</sup> Its use as an adjuvant to liver extract has as yet no rational basis, adds materially to the expense of treatment, and may unpredictably alter the dosage requirements for liver extract.

Iron therapy is usually not indicated, for, barring the existence of a chronic bleeding lesion, the iron stores are ample. The development of hypochromia in the course of a remission, induced or otherwise, is an indication for iron therapy, it is also the signal for an intensive search for a bleeding lesion bearing in mind the unusual susceptibility of these patients to the development of gastric carcinoma.<sup>25</sup> The use of hydrochloric acid rarely affords symptomatic relief of dyspepsia and diarrhea, which are characteristic of pernicious anemia in relapse, but which spontaneously disappear when a therapeutic remission has been accomplished.

#### TREATMENT OF NUTRITIONAL MACROCYTIC ANEMIA

Patients with this type of anemia, in contrast to those with pernicious anemia, do not invariably obtain a satisfactory clinical or hematologic remission following parenteral injections of refined liver extracts, however intensively this treatment is applied. Certain of these refractory cases are improved when cruder extracts are administered,<sup>28, 29</sup> in rare instances only, when the crude liver extract is received by mouth. Folic acid, the effectiveness of which has been convincingly demonstrated in the treatment of tropical sprue<sup>30 31</sup> and the macrocytic anemias associated with pregnancy and infancy,<sup>31</sup> may eventually be established as the agent of choice for the correction of most, if not all, deficiency anemias classified in this category.

The logical therapeutic approach, applicable in all cases of macrocytic anemia, first of all entails the establishment, or exclusion, of primary pernicious anemia as the etiologic diagnosis, inasmuch as maintenance therapy is rarely required in cases other than pernicious anemia. The discovery of free hydrochloric acid in the gastric juice, in addition to signs indicating gross dietary inadequacy or other factors known to promote the development of this blood picture, usually provides adequate confirmation of the diagnosis.

A therapeutic trial with refined liver extract is appropriate, a schedule of treatment being devised, analogous to that employed in the treatment of pernicious anemia. A diet providing a high protein intake supplemented by materials that are effective sources of the vitamin B complex should concomitantly be received. If a hemopoietic response does not result, folic acid should be administered in dosages recognized to be generally effective, i.e. 50 to 150 mg daily for at least ten days when the presence or absence of refractoriness to this agent will have been established. If a remission is evidently in progress the drug should obviously be continued, its dosage eventually being reduced to more economic levels, e.g. 5 to 20 mg daily by mouth.

It is difficult in most cases to predict with any degree of certainty the character of the hematologic response to specific therapy; a significant proportion of cases, notably those with nontropical sprue, proving quite refractory to folic acid<sup>22</sup> as well as to other drugs and nutrients. Every effort should be made to discover and correct any factors that potentially interfere with those metabolic processes relating to erythropoiesis, attention being specifically focused on possible sites of chronic infection and possible lesions involving the gastrointestinal tract.

#### TREATMENT OF HEMOLYTIC AND AREGENERATIVE ANEMIAS

Palliative transfusions afford the only therapy of benefit in certain hemolytic disorders and in cases with anemia of the aregenerative type. Maintenance of physiologic red cell concentrations by this artificial means may be permanently required in severe proximal nocturnal hemoglobinuria, acquired hemolytic jaundice, the leukemias and lymphomas, and in aplastic anemia due to whatever cause.

Splenectomy is a therapeutic device of great value as a method of curtailing at least temporarily the rate of blood destruction in idiopathic acquired hemolytic disease of the type in which adsorbed anti-red cell antibodies are demonstrable by the Coombs test.<sup>19</sup> This operation is almost invariably indicated in cases of congenital hemolytic jaundice with anemia despite the fact that the inherent defect characterizing that disease involves the erythrocytes rather than the spleen. Premature destruction of these abnormal red cells is chiefly promoted at that site where they are selectively retained, become segregated from the circulating plasma and rapidly deteriorate.<sup>21</sup> Transfusion therapy administered in anticipation of splenectomy should supply no more than the minimum quantity of blood consistent with a safe pre-operative preparation. For an undesirable consequence of transfusion in many such cases, is an increase in splenic retention of the patient's



## THE CARE OF PATIENTS PARALYZED AS THE RESULT OF INJURY TO THE SPINAL CORD AND CAUDA EQUINA

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For the proper care of patients who have been paralyzed as the result of an injury to the spinal cord or cauda equina cooperative teamwork on the part of many specialists is essential. In addition it is equally essential that some member of the team act as coordinator and leader. It is of no importance which member is so designated provided only that he is enthusiastic, interested, persistent, possessed of great patience and above all imbued with the conviction that all such patients can be made into useful, virtually normal members of the community again in spite of their physical handicaps. Due weight should be given, however, to the fact that in the last analysis these patients are surgical problems and are afflicted with a lesion of the nervous system. Whoever is chosen must have at all times the interested active collaboration of his patient and the patient in his turn must be equally endowed with the will to rehabilitate himself. The latter must also meet certain physical requirements. For example his shoulder, arm and hand muscles must be normal and capable of being built up to a point where they can lift his weight with the help of crutches. He must be intelligent enough to appreciate the value of the strenuous reconditioning he needs and to put into practice the necessary bladder and bowel training. He must have ambition and initiative enough to withstand the well meant but misdirected efforts of his family and the community to limit his activities and thus to spare him from the constant small annoyances of our present-day life. He must be thick skinned and have enough self respect to be willing to accept employment offered him as charity and energy and interest enough to prove to his employer that the charity was needless and that he can compete successfully on the basis of his accomplishments alone with his nonparalytic fellow workers. Finally he must have financial backing enough to be able to afford to spend from eighteen to twenty four months in a hospital and an ambulation class and in addition meet all the contingent medical and surgical expenses that must needs arise in the treatment of such a complicated condition.

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These requirements actually are no more than any seriously ill or injured patient has to meet, the only difference being that they extend over a longer time, that they demand more initiative and patience on the part of both the patient and the doctor and that the possibility that such effort is worth while is not generally recognized in either the medical or lay community. The attitude of defeatism that is still widespread among all who have to do with the welfare of "paraplegics" has no justification now. It can be stated unequivocally that, provided he has the use of his arms and hands, is intelligent and co-operative and is willing to give the necessary time and effort, any patient who has been paralyzed to any degree as the result of an injury to his spinal cord or cauda equina can now be assured of rehabilitation to a point where he will have full twenty four hour control of his bladder and bowel and where he will be able to lead a normal social and work life within the limits prescribed by any necessary use of braces and crutches. He will be free of bedsores and will require neither hospitalization nor special nursing care after his rehabilitation has been completed. His life expectancy should not be materially shortened, provided he uses ordinary care and does not substitute bad habits for those good ones he has been taught during his rehabilitation. These ends can be met more easily and more promptly if the patient is properly treated from the start. They can also be reached, however, at any time up to a number of years after the accident provided such permanent structural changes as osteoporosis, stag-horn renal calculi, a fibrotic contracted bladder, hydronephrosis, hydroureters, and osteomyelitic destruction of the heads and necks of the femurs and of the acetabula have not occurred.

### DIAGNOSIS

To avoid misunderstanding it may be well to mention briefly the diagnostic criteria on which therapy should be based.

1 *Spinal Shock*—This is present in all significant spinal cord injuries for a variable length of time. It does not accompany injuries of the cauda equina. The signs and symptoms are those of chaotic visceral and somatic areflexia. Its pathology is unknown. The bladder is atonic and there may be paralytic ileus. There is a tendency to bedsores and hypoproteinemia.

2 *Anatomic Transection Of the Cord*—There is a complete division of all structures of the cord at some point. Artificially induced electrical impulses do not pass through the damaged area. There is a total loss of all sensation and voluntary motion below the level of cord

injury, with either spastic or flaccid paralysis. There are frequent but not constant involuntary flexor or extensor mass spasms of the legs, low back and abdomen. The bladder and bowel will be reflex in type. The sphincters will be reflex in type except in patients that have been mistreated. The bladder sphincters may be spastic and hypertrophied in such patients. There may be either a positive or a negative Queckenstedt test.

*Of the Cauda Equina*—There is a complete peripheral nerve type of sensory and voluntary flaccid paralysis which involves the legs. The bladder and bowel will be totally denervated and the bladder autonomous in type. The sphincters may be flaccid and atonic. In badly treated cases the bladder sphincters may be hypertrophied and spastic. There are no spasms. Root pain is a frequent symptom.

3 *Physiological Transection Of the Cord*—The cord need not be grossly severed. Artificially induced electrical impulses will pass through the damaged area of the cord but will only cause ineffective responses in those muscles that are supplied by the spinal segments below the injury. Traumatic syringomyelia, atrophy and necrosis with scar replacement are common forms of physiologic transection. There is a complete sensory and voluntary motor loss with flaccid paralysis below the level of injury. There are no involuntary spasms. The bladder and bowel will be reflex in type. The sphincteric response will be physiologic except in badly treated cases. In these the bladder sphincters may be hypertrophied and spastic. There may be either a positive or negative Queckenstedt test. *Physiologic transection of the cauda equina* does not occur.

4 *Partial Injury Of the Cord*—The cord is partially damaged by edema, hemorrhage, thrombosis, necrosis and/or compression. Hematomyelia, edema, contusion, traumatic syringomyelia, the Brown-Séquard syndrome, isolated intramyelogenous hemorrhage and compression with or without any of the above are various types of partial cord injury. Artificially induced electrical impulses pass freely through the damaged area in the cord and cause active contractions in the muscles supplied by the spinal segments below the level of injury. The intramyelogenous damage has a tendency to spread both upward and particularly downward for many segments from the point of maximum injury. There will be a wide variety and distribution of sensory and voluntary motor loss. Paralysis will usually be flaccid in type but may be spastic in appearance when associated with involuntary spasms. There may be disabling involuntary flexor or extensor spasms in the arms, legs, back and abdomen even though voluntary



motion may be largely retained in the area that goes into spasm. The bladder and bowel and their sphincters will be normal. There may be either a positive or a negative Queckenstedt test.

*Of the Cauda Equina*—There will be a wide variety of sensory and voluntary motor loss of a peripheral nerve type. When there has been a major fracture of one of the lumbar vertebrae, this paralysis is apt to appear first ten to fourteen days after the injury. It is caused by compression of the roots that make up the cauda by organizing blood in the lumbar subarachnoid space. The bladder and bowel may be either normal or denervated and autonomous. The sphincters may be flaccid. The Queckenstedt test may be either positive or negative or first negative (with bloody cerebrospinal fluid) and later positive.

5 **Injury of the Sacral Segments of the Spinal Cord.**—This may be either a transection or a partial injury and differs in no way from the descriptions given above except that if it is a transection the bladder and bowel are denervated and the bladder is autonomous in type. The external sphincters may be flaccid and atonic.

6 **Concussion Of the Cord**—This is present only as the result of a gunshot wound in which the missile damages some part of the bony wall of the spinal canal but does not come into actual contact with either the meninges or the cord itself. This may produce either a transection or a partial cord injury as described above. *Concussion of the cauda equina* is not known to occur.

7 **Sexual Status**—Nothing is actually known about the effects of cord and cauda equina injuries on the sexual status of the individual. Investigation has been started however, and it is already apparent that most if not all of what is accepted as fact today in regard to this important function is based on surmise and has no relation to the few facts that are known.

To rehabilitate these patients with traumatic spinal paralysis in accordance with the criteria set out above, it has proven necessary to compartmentize their treatment. In consequence it is now the custom in my clinic at the Boston City Hospital to classify them for therapy in six groups. This same system has been established and used with success under my direction at one of the Veterans' Administration Paraplegic Centers. This classification with its composite details is outlined below. It was developed as the result of experience with 330 patients seen in the past seventeen years on the Neurosurgical Service at the Boston City Hospital. More recently it has been used with satisfaction on some 250 or more patients at Cushing General Hospital under the auspices of both the Army and the Veterans' Administration.<sup>1</sup> As experience has increased, it has become more and more ap



may already exist in the patients under consideration. Because of the presence of spinal shock and its effect on the visceral reflexes the bowel and bladder become paralytic and atonic. If neither organ is allowed to distend, this, of itself, will do no harm. Distention of the bowel can only be prevented by stopping the ingestion by mouth of all food and fluids, including water. Intravenous feeding may be substituted. The use of a Miller-Abbott tube with or without Wangensteen suction may be necessary and life saving in neglected cases or if, as frequently happens in severe multiple injuries, the stomach is distended also. This treatment should be continued until peristalsis is again audible and should be started at once after the accident. It replaces the old therapy of turpentine stupes, enemas and prostigmine. Abdominal exploration in these patients while they are distended is contraindicated unless the surgeon is prepared to accept the risk of having to perform an otherwise useless enterostomy in his efforts to replace the distended paralytic bowel.

Distention of the bladder will also decrease the efficiency of the diaphragm in its efforts to carry the full respiratory load. It is prevented by the insertion of an indwelling catheter through the urethra. A suprapubic cystostomy and especially a perineal urethrostomy are both contraindicated, unnecessary and harmful. The catheter should not exceed 16 F in size and it is preferable not to use a Foley type. A cystometrogram should be done at once and if possible the catheter attached to a tidal drainage apparatus.<sup>2</sup> If this is not possible the catheter should be left open and the bladder kept empty by constant drainage. The older methods of emptying the bladder by manual compression through the abdominal wall or by allowing it to fill and overflow are accompanied by a tremendous incidence of infection of the genitourinary tract and death and are now thoroughly discredited.

The use of oxygen mixed with inspired air is essential. This should be given through a nasal or oral tube. Attempts to administer the gas through a mask will fail because these patients will not tolerate anything that has the appearance of interfering with their respiratory efforts. If the doctor persists in his attempts to use a mask, the nervousness, restlessness and increased metabolism that result more than offset any good that the oxygen may do. It is for this same reason that respirators do harm rather than good in these patients. Respiratory problems do not arise in cauda equina injuries.

**The Cerebrospinal Fluid**—It is necessary to be familiar with the characteristics and dynamics of the cerebrospinal fluid in these patients if their future treatment is to be properly planned and if they are to be in a position to get a maximal return of function. A lumbar

puncture with a Queckenstedt test should be performed at the earliest possible moment after the injury. Compression of the jugular veins is best exerted by a graduated measured rise and fall of pressure in a sphygmomanometer cuff that has been wrapped about the neck. A specimen of cerebrospinal fluid should be examined for fresh blood (especially in the cases with injury to the cauda equina and most especially in patients with major fractures of the lumbar vertebrae, even in the absence of neurologic signs and symptoms) and protein content. If no block can be demonstrated then decompression of the cord or the cauda cannot be advanced as a reason for laminectomy. If there is a partial block frequent repetition of the test must be carried out to settle whether or not a complete block is developing. If there is a total block decompression by an adequate laminectomy with opening of the dura and relief of the block should be done. The only problem that remains to be settled is to decide when the operation can be done with a minimal amount of risk to the patient and a simultaneous minimal length of compression of his cord or cauda. Blood in the cerebrospinal fluid without a block requires daily or twice daily lumbar drainage of all the bloody cerebrospinal fluid. It is possible and reasonable to obtain until such time as its total protein has returned to normal. An increase in total protein in a specimen of cerebrospinal fluid from below the damaged area indicates at least a partial block.

**The Associated Bone Injury**—The associated bone injury should be treated by hyperextension with or without traction. The hyperextension must be slow and increased gradually as indicated. It is well to remember at this point that this discussion has to do with a patient whose bone injury is secondary to his cord injury and that methods that are accepted and acceptable in the treatment of similar bone injuries in patients who do not have a cord injury not only do not apply but are lethal in a high percentage of the former cases. It is for this reason that rapid hyperextension is ruled out. It is for the same reason that plaster of paris cannot be used. This is particularly true in the cervical and thoracic cord injuries—that is, in the injuries that have the greatest respiratory difficulties. A diaphragm that is only just able to carry its load will give out when it is forced to aerate the lungs if and when they are enclosed in a heavy immobile shell. Moreover plaster of paris casts or any splint that is immovably fixed in relation to weight bearing points on the surface of the body will cause necrosis of the tissues squeezed between the cast on the one hand and the bone on the other. This occurs because of the loss of the normal skin vascular reflexes that otherwise compensate for any local pressure

ischemia In the former case first pressure sores and then immediately bedsores develop, with all the attending difficulties of loss of serum, hypoproteinemia, infection, toxicity, anemia and friable scars that inevitably follow

**Pressure Sores and Bedsores**—Bedsores should never occur in a properly cared for patient. When they do occur they are always preceded by pressure sores If pressure sores are to be prevented persistent unremitting care of the skin over all weight-bearing bony points and especially over the sacrum, ischii and trochanters must be provided As pointed out above, the presence of an abnormal skin-vascular reflex renders the skin in these regions particularly susceptible to pressure ischemia and necrosis This is true even when plaster of paris casts or other fixed splints are not used For that reason it is imperative that weight-bearing over any bony prominence be limited to such an amount as will be less than lethal to the local tissues Experience has shown that continued weight bearing cannot be extended beyond two hours at a time without risk of producing pressure necrosis For this reason all patients with spinal cord injuries must be turned at two hourly intervals as long as they are bedridden As further prophylaxis they should be kept on a foam-rubber mattress They must be kept dry and clean, especially in regard to the skin over their back Even as short a time as fifteen minutes spent lying in a wet bed will macerate the skin sufficiently so that it will break down in less than the two hour interval and a pressure sore be caused Proper nursing attention is of the utmost importance to prevent this but no less important is the use of tidal drainage This not only controls leakage of urine but eliminates most of the otherwise constant nursing that will be necessitated in its absence Especial attention must be given to the patients with thoracic and lumbar cord injuries Cord damage at these levels interferes more and for longer periods with the sympathetic pathways over which the impulses that normally govern the skin-vascular reflex pass and hence render the patient more liable to pressure sores

**Diet**—Major spinal cord injury cases develop a nitrogen deficit with reversal of the normal albumin globulin ratio as part of the generalized effect of the trauma Hence such patients lose weight and have their nutritive processes badly hampered These phenomena are increased if there is an open wound from which serum with its high protein content exudes constantly To return their nitrogen balance to normal their caloric and protein intakes must be greatly increased They must ingest a minimum of 3000 calories and 150 grams of protein every twenty four hours, and all of the vitamins must be given

in large doses. They are also prone to develop anemia and therefore sufficient blood to maintain their hemoglobin and red blood count at approximately normal levels must be administered by transfusions.

**Fluids.**—Any patient whose genitourinary tract is as seriously affected as is the case in these patients needs large amounts of fluids to keep his urine dilute and his tissue fluid reservoirs filled. A minimum of 4500 cc. of fluid in addition to that included in the diet must be administered every twenty-four hours to meet these requirements. This level should be maintained until the function of his genitourinary tract has reached its end point of recovery after which it should be reduced to 3600 cc. in twenty-four hours. In this latter instance especially if the patient is undergoing bladder training the fluid should all be ingested at the rate of 300 cc. per hour between 7:00 A.M. and 7:00 P.M. The fluid should be given preferably in the form of water and through the mouth. If that is impossible the patient may be fed through an indwelling stomach tube or the fluids given in whole or in part by vein in the form of 10 per cent glucose dissolved alternately in isotonic salt solution and distilled water.

#### SPECIFIC THERAPEUTIC REQUIREMENTS

Other than these general universally applicable immediate therapeutic measures treatment of patients with injuries to the spinal cord and cauda equina can be divided into six categories or classes. It is in these groups that the specific methods of treatment are applied.

To reach its maximum effectiveness the need for this classified therapy must be apparent to not only the physician and the patient but above all to that member of the department of physical medicine who is directly in charge of teaching ambulation. All however must understand the philosophy behind the therapy in order to instill and to absorb the successive details of training. Only thus will the patient profit most.

The first three classes are devoted to getting the patient into the best possible physical shape to learn ambulation and end with the patient active in a wheel chair. The fourth class has for its philosophical background the instillation of *confidence* in the patient. He must be confident, for example, that his braces and crutches will actually support him and that taking both feet off the floor at the same time does not mean disaster. Without confidence he can never ambulate to his full capacity with it he advances rapidly to greater and greater facility. Having acquired confidence and the ability to move about his next training is devoted to the building of *endurance* and its corollary strength. This occurs in class five. Without these attributes

his mobility will be so limited as to be impractical—with them he has normal but unskilled mobility. The sixth and last class is devoted to teaching the *skills* of advanced mobility. A confident patient with good muscles is ready for complicated activities. With this learned he has become a virtually normal ambulator and is again a self-respecting, self-supporting member of his community.

**Class 1**—This is the stage of Surgical and Spinal Shock. The patients enter this class with the receipt of their injury and remain in it as long as surgical shock is present. This may be for only a few hours in the less severely injured. In the more serious injuries and especially in the cervical cases, however, actual or potential surgical shock may be present for days. Operative procedures, manual reductions and similar treatments carry an extremely high mortality during this stage and are contraindicated. On the other hand, spinal shock may last for a long time and extend into Class 2. This is especially true in the presence of a major infection, hypoproteinemia, anemia, malnutrition, or exhaustion. It may disappear only to return with the advent of any of the above conditions at any later date. The development of a large septic bed sore or pyelonephrosis, for example, or the necessary performance of a major surgical operation will cause spinal shock to recur and remain until the patient's metabolic processes are again established at normal and he is in the first stages of ambulation. Treatment during this first stage will be as outlined in the preceding section, supplemented by any necessary supportive measures. In cases that have been properly treated from the start, this stage of surgical shock will last on the average from seven to fourteen days. Spinal shock will also be present during that time. When spinal shock recurs later following major surgery it will last only from two to seven days, after which the patient will pass rapidly through the intervening succeeding therapeutic stages until he is again in the class that he occupied before the spinal shock returned.

**Class 2**—This is the stage of Diagnostic and Reparative Surgery. As a prerequisite to these procedures any nutritional deficiency must be corrected and the patient be definitely "on the mend" and in nitrogen balance. As an aid to meeting this fundamental requirement skin grafting of large weeping ulcers may be imperative. This is not definitive therapy, however, and is used only as a means to an end.

With the patient well nourished and gaining weight, the need for a more accurate diagnosis by visualization and electrical stimulation of the cord can now be met by an exploratory diagnostic laminectomy. With the diagnosis of an anatomical transection of the cord estab-

lashed by visualization and electrical stimulation at a diagnostic laminectomy any spasms or mass reflex that is present can now be eliminated by the performance of an anterior dorsolumbar rhizotomy. Those patients whose cords or cauda still show evidence of being compressed by the demonstration of a positive Queckenstedt test can have a decompressive laminectomy performed at this time.

In the absence of spasms either because they have never been present or because they have been eliminated by an anterior rhizotomy repair of bedsores may be undertaken. In general this should be done in such a way as to leave behind a padded area with a minimal nonadherent scar over the bony prominence. This may require the swinging of large flaps and will certainly require radical excision of all infected bone as well as any scars that are adherent or covered only with a layer of epithelium and no subcutaneous tissue.

Repair of bladder fistulas and other genitourinary operations together with such minor orthopedic procedures as peripheral nerve and tendon operations that are directed toward the relief of abdominal and other minor spasms may be undertaken also during this stage. If by chance previous therapy has been so bad as to permit osteomyelitis or nutritional necrosis of the heads and necks of the femurs and the cavities of the acetabula necessary excision and drainage of the septic joint and possible implantation of a Smith Petersen cup<sup>2</sup> may be carried out.

It is during this stage that the *bone injury* heals. Hyperextension traction and other methods looking toward that end must be maintained and modified in accordance with the appropriate x ray indications. The surgeon should be cautioned again however relative to the dangers of using plaster of paris or other fixed splints in these cases.

The *bowel* is controlled by enemas. During this stage bowel training in its simplest form should be begun by giving the enema daily at the same hour.

The *bladder* is maintained on tidal drainage. This is adjusted with the help of weekly cystometrograms to the stage of recovery that has been reached by the organ at the time of the test. By the time the patient is ready to move to Class 3 the bladder will have reached a reflex (so-called "automatic") stage in the transected cases and a normal level of activity in the partial cases provided it and its sphincters have not been denervated.

If the motor paralysis is of a flaccid type and whether it is complete or not *physiotherapy* with massage active and passive assisted



motion and maintenance of joint freedom should be started early and pressed actively. Physiotherapy is harmful and contraindicated if the paralysis is of the spinal spastic type, however.

*Occupational therapy* of a short range diversional character with easily accomplished projects should be started during this stage.

As soon as the bone injury is healed sufficiently to permit active motion in bed the simpler bed exercises are started. It is at this point that all *special nursing* must be discontinued. Failure to do so eliminates that essential stimulus that comes from self care. It is particularly important to elicit this stimulus at the earliest possible moment because of the devastating psychological effect and the permanence of the injury. For this same reason the patient should be moved out of any private or semiprivate accommodation that he may have had in the hospital up to this point and be put instead in a large ward. This will apply regardless of his social or financial status.

Where possible *bed exercises* should start with the patient learning to turn himself in bed and to feed himself. As his bone injury becomes more firmly anchored and with the aid of a back splint if necessary, he can then gradually increase the scope, severity and length of his exercises. Deep breathing exercises, push-ups from a prone position, work with dumbbells and spring exercisers to develop hand grip, shoulder, upper arm and scapular muscles, the setting of abdominal and back muscles as well as a number of other similar procedures, should be practiced regularly in accordance with a well-planned schedule. These activities save much time later on when ambulation is actually begun.

The patient remains in Class 2 until such time as the bone injury is sufficiently healed to permit him to bear weight on it and to be upright or, if there has been little or no bone injury, until all diagnostic or reparative surgery is completed. Depending on these factors as well as the severity of the cord injury, this stage will last from two to eight months.

**Class 3**—This is the stage of **Wheel-Chair Mobilization**. The bone injury will be healed sufficiently to allow the patient to remain upright either with or without a back splint. All diagnostic and reparative operative procedures will have been completed. The patient will be free of bedsores and will have no or at most only minimal spasm. His bladder will be reflex if the cord injury has been a transection and normal if the cord injury has been a partial one and provided it and its sphincters have not been denervated. In this latter case the bladder will have become autonomous. The patient is now ready to get out of bed.

Formal *bowel training* should be started during this stage. The patient should go to stool at the same time every day. Evacuation should be aided at first by daily enemas. These will be decreased, mild saline cathartics being gradually substituted for them, and the commode and then the toilet replace the bed pan until by the time he is ready to leave this class for the next one he will be moving his bowels once every twenty-four or forty-eight hours only, without enemas and with only occasional mild catharsis at the time that he has chosen at the start of his training.

In the patients with partial cord injuries the bladder should be normal by this time. If it is not, it will be because of neglect in treatment during the previous stage or because of denervation. The latter is extremely unlikely and should not be accepted as a final estimate of the situation without careful review and checking of the evidence. Bladder training as applied to reflex bladders must be tried, and if the organ has been allowed to shrink through mistreatment, efforts should be made to stretch it with properly adjusted tidal drainage. If there is a large amount of residual urine and there is nevertheless cystometric evidence that the bladder activity is reflex, the patient should get out of bed, start his mobilization, and try bladder training before any operative procedures will be indicated. In particular, resection of the bladder sphincters should not be countenanced at this time. After all, the need for this destructive procedure arises either out of a condition that is the aftermath of improper earlier bladder therapy—that is, spasm and hypertrophy—or because of an obstructing prostate which presents its own indications for therapy regardless of the associated neurologic condition. If patients with cord injuries have their condition accurately diagnosed and it and their bladders properly treated by tidal drainage from the time of injury, there will be no indication or reason other than an obstructing prostate for resection of the neck of the bladder.<sup>1</sup>

Bladder training, which has been fully described elsewhere,<sup>4</sup> should be started during this stage on all patients who are suffering from a transection and whose bladders are reflex—that is, automatic. It is important to appreciate that an automatic bladder is not as good an end result as it is possible to get for these patients. With intelligence, perseverance, and patience on the part of both the doctor and the patient, an automatic or reflex bladder can be transformed into a *controlled* reflex bladder. With a controlled reflex bladder the patient will not have to wear any apparatus, will keep dry and clean day and night, can go without emptying his bladder for at least three hours during the day and throughout the night without waking or getting wet and

has virtually a normal bladder. This is quite different from the facilities provided by an automatic bladder.

Patients whose bladders have been denervated cannot usually count on profiting from the advantages offered either by the automatic or the controlled reflex bladder. However, since this is not universally true they should be given a chance to see what can be done by bladder training. If it fails they will have to wear an indwelling catheter constantly and use tidal drainage at night. Patients with denervated atonic bladder sphincters or in whom incontinence has been produced by so-called resection of the bladder neck or internal sphincter for spasm or hypertrophy have no choice but to resign themselves to the permanent use of a urinal. Even with a catheter in place, they leak urine as soon as they stand erect. No surgical method is as yet available for correcting this sphincteric loss.

*Physiotherapy and occupational therapy* should be continued as before.

*Bed exercises* should be continued and increased in scope and severity. The patient must now learn to sit erect in bed without support, to flex forward at his hips until his chin is virtually on his knees, to wash and dress himself completely, to get on and off the bed pan, to move himself freely in bed and to do all this without help. In addition, he must learn to get from bed to wheel chair and back, and from wheel chair to floor and back. With these skills accomplished he will then easily learn to get from the wheel chair to the toilet or into the bathtub and back without help.

He is now mobile in a wheel chair and completely able to care for himself as far as his personal needs go. However, he still needs his muscular development increased in his shoulders if he is paraplegic and wants to walk and he still needs development through use of his weakened muscles if he is only a partial cord injury. For this purpose *mat exercises*, one hour at a time up to the point of physical tolerance are begun during this stage. These exercises are done on a gymnasium mat on the floor and preferably in groups. Among others they include short-crutch walking, certain balancing exercises, four legged progression, crawling, push-ups, forward bends, three point balance and "peanut-rolling." Training in getting from a wheel chair to the floor and back again is also included. Partially paralyzed patients will have to have the exercises modified or increased in accordance with their individual needs.

It is or should be apparent now why the continuance of *special nursing* and *isolated housing* is bad for these patients.

It is during this stage that the patients are measured for appropriate

*braces* and those that need them are provided with *wheel chairs*. In spinal paraplegics the basic brace is a bilateral leg caliper with a foot drop support and a gravity knee lock.<sup>\*</sup> This is applied without modification to all patients with their transection at the eighth dorsal segment or lower. Under certain circumstances such as abnormal position or mobility of the lumbar spine some of these patients will have to have a padded metal pelvic band added to the calipers. This should be attached by free swinging nonlockable hinge hip joints placed at the level of the trochanters. For patients with transections between the first and eighth dorsal segments a low back brace with an anterior abdominal pad is added. The brace is attached in the same way that the pelvic band is. For cervical lesions that have enough musculature to sit upright the Zimmer brace modified so as to include a pelvic attachment should be used. If bilateral calipers can also be of use on his legs and such a patient is able to stand this brace is used separately.

During this third stage the patients are taught bladder and bowel control, are mobilized in a wheel chair, learn to take complete care of their personal needs, have their crutch walking and other muscles developed and are provided with whatever braces and wheel chairs they may need. This stage usually lasts from one to three months.

**Class 4**—This is the stage of Early Ambulation. The object is to teach confidence. Patients entering this class have bladder and bowel control, can take full care of themselves, are mobile in a wheel chair and have had their musculature adequately developed. They are equipped with the necessary splints. It is during this stage that the patient learns ambulation up to and including the swing through crutch gait as well as all simpler varieties of aided ambulation.

*Physiotherapy* is now stopped. *Occupational therapy* as a diversion should be stopped as well and that activity channeled into training that will lead to productive skills, wage earning and self support in the future.

*Mat exercises* are continued and increased in scope, length and severity. The patient is fitted to *crutches* and learns to put on and take off his own *braces*. He is then started on *crutch balancing exercises*. These are done both against the wall with crutches and between parallel bars without crutches. With this learned he progresses through a shuffle and swing to gait, crutch balancing away from the wall, turns, swing through crutch gait and if possible two- and four-point walking.

It is during this stage that *residual spasms* may become apparent. If they interfere with ambulation they may have to be dealt with surgically. For example, psoas spasms that jackknife a patient when an

bulating may require peripheral neurectomy on several intercostal nerves and scissoring or lagging of one leg will require peripheral denervation of the adductors, a tenotomy, or some other similar operation. These procedures should be carried out at this time without delay and as soon as their need becomes apparent. Procrastination only adds to the difficulty. This is particularly true when it takes the form of attempting to control involuntary motions that are stimulated by splint restriction, by such devices as locked hip hinges, fastening the caliper splints together with a metal bar at the ankle and similar makeshift procedures. They will all correct in some fashion the difficulties that are basically traceable to the spasm, but at the same time they prevent the acquisition of further ambulation skill and that personal freedom which would be obtainable otherwise. *Curare* is ineffective as a means of doing away with such spasms.<sup>6</sup>

Some of the patients may also complain of *pain* which takes so much of their attention that their progress is retarded. This pain may be of any type but during this stage attempts to do away with it should be limited to procedures that are not destructive. This usually means that only vasospastic and root pains or those indefinite sympathetic system symptoms that are associated with bladder distention<sup>7</sup> can be treated. Such procedures as paravertebral or peripheral nerve injections of novocain or alcohol and the administration of tetraethylammonium chloride are justifiable and frequently curative. It may even be advisable to explore an injured cauda equina at times. Cordotomy should not be done at this early stage. Too many of these patients get adjusted to their pain as their activities and interest increase and what was complained of originally as an unbearable pain becomes first of all bearable and then gradually sinks to the level of only an annoyance.

This fourth stage merges imperceptibly with the next one. Its length varies with the patient, the instructor and the facilities for training but usually it lasts from two to four months. If facilities for training and instructing personnel are better outside of the hospital than they are inside, the patient can now be discharged, live in a hotel or boarding house and attend ambulation classes wherever the best ones are held. This usually will require the services of an attendant, however, who need not and indeed should not be a trained nurse but rather a person who is willing to act chiefly as a "prime mover." His only duty is to get the patient in his wheel chair from his room and through the streets to his destination with the aid of any necessary public conveyances. In particular, he should not usurp any of the personal care and mobility skills that the patient has already acquired.

**Class 5**—This stage merges imperceptibly with the preceding. It is the stage of *Intermediate Ambulation*. It is devoted primarily to increasing the patient's *strength* and *endurance* so that he can bring to practical use the skills he has learned in Class 4. *Mat exercises* are now increased still further and increased *social and work activity* is also demanded by increasing further the amount and degree of difficulty of *ambulation*. The patient learns to turn around, walk sideways and backwards and to mount low curbs and ramps. He learns now to get in and out of automobiles. He must be able to wear his braces all day, to walk 150 yards without stopping, to walk on all kinds of terrain and must walk to and from all meals and other activities. He must be able to cross a mock up of a standard street within the traffic light limits, cover 100 yards in a given time, open and close doors, answer a telephone while standing erect, learn to drive a specially equipped automobile and similar activities in his braces and without evidence of fatigue.

If his *pain problem* is one that justifies it and that can be expected to respond to that therapy, a *cordotomy* is now permissible. It should be done in the first or second thoracic segments instead of at the usual site, should be bilateral and should produce analgesia in all non-anesthetic areas below about the fourth dorsal segments.

By this time, provided the patient has learned his lessons well, no further operations will be necessary. This stage will cover another two to four months and is the crucial stage with the paraplegics as far as their future is concerned. Many will want to stop here and a number will. If they do, they will not have attained their full activity or skills and will some day regret not having done so. Every effort should be made to persuade them to continue to full ambulation. To that end earnest attempts should now be made to obtain *gainful employment* for them. They are now socially acceptable but are not capable of competing at *gainful labor* with their fellow workmen except in a very limited capacity. Because they have been injured is no reason why they should either be deprived or be allowed to deprive themselves of the chance to be fully self-supporting, but rather, having in mind all the factors, it is a reason why they should be assured of employment if they demonstrate their employability by their persistence and initiative. Failure to employ these paralvics burdens the community with the expense of their maintenance, destroys the patient's individualism and substitutes that despicable hypocrisy of our modern civilization—enforced charity—for self-respect through self-support. The patient must be expected to contribute his efforts to attain complete ambulation as his share towards preventing this tragedy.

**Class 6**—This is the final stage and is one of Advanced Ambulation. In it the patient acquires skills. All that has been learned up to now in the classroom is practised in public, at first with the help of an instructor and then alone. Shopping trips, walks in crowds and traffic, visiting restaurants, actual employment of automobile, taxis, buses, street cars and railroad trains and overnight stops in a hotel are all undertaken, together with many other activities. These include learning to get up to an erect position from the ground without help after a fall, walking over rough terrain, getting up and down all types of stairs and steps with and without hand rails, getting in and out of all types of chairs and theater seats, getting himself and his chair in and out of his automobile without help, walking 1000 yards without stopping, and other similar activities. This stage will take six or eight weeks and should be undertaken without the attendant mentioned under Class 4. Hereafter, the patient will be able to lead a full social and work life, to live in any modern house without having alterations made in it, and to be a useful, active, productive, self-supporting member of the community without special privileges or attendance and in spite of what appeared at first to be and what has been but is no longer a completely disabling and usually lethal injury.

#### SUMMARY

The important features of the modern therapy now available for the rehabilitation of patients paralyzed as the result of an injury to the spinal cord or cauda equina are described.

Emphasis is placed on the fact that all such patients, if properly treated, can now be rehabilitated to the point where they can be assured of a normal social and work life within the limits imposed by any necessary braces and crutches. Moreover, if they cooperate intelligently their life expectancy will not be materially altered.

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# REPAIR SOLUTIONS IN THE TREATMENT OF METABOLIC ACIDOSIS AND ALKALOSIS

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## INTRODUCTION

Selection of proper parenteral fluids for the treatment of metabolic acidosis or alkalosis has been discussed frequently.<sup>1-3</sup> The principles of such therapy have been defined by extensive investigations during the past three decades.<sup>4-6</sup> Until recently treatment of water and electrolyte imbalance in most clinics has been directed towards correction of abnormalities of the extracellular fluid space and in most patients this is sufficient. Evidence is accumulating that in certain instances rational therapy of dehydration and the accompanying electrolyte abnormalities can best be effected by additional consideration of losses from and by providing replacements for the intracellular fluid and electrolytes.<sup>6,7,8,9,10</sup>

Estimation of the type and quantity of parenteral solution necessary for the treatment of metabolic acidosis or alkalosis requires careful evaluation of both the clinical and laboratory findings of each individual patient. First, an attempt at calculation of the deficit of body water must be made for dehydration almost invariably accompanies either condition as encountered clinically. In the majority of patients in whom total body water has been depleted as a result of direct losses through the urine, the gastrointestinal tract, the lungs, or the skin, it is the extracellular fluid space which ordinarily is first contracted. This fluid compartment may be depleted further by shifts of water into the cells in response to lowering of osmotic pressure in the extracellular space if there has been a greater relative loss of extracellular electrolyte than extracellular water. Particularly after water replacement has been started, these shifts may be so extensive that total body water is normal although extracellular fluid volume is still grossly reduced.<sup>10</sup> The water deficit may finally include significant losses of intracellular fluid. Second, losses of electrolytes must be cal-

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culated as closely as possible, for it is the relative quantities of anions and cations remaining in the extracellular fluid which determine the presence of acidosis or alkalosis

The water deficit may be very difficult to assess. Since during dehydration the concentration of extracellular electrolytes, initially at least, is maintained at the expense of extracellular fluid volume, electrolyte concentrations in the serum are often altered only after total extracellular fluid has been considerably reduced. Hence serum anion and cation concentrations may be normal in the presence of considerable water loss. Abnormal concentrations usually indicate considerable water depletion, but do not necessarily quantitate it. Clinically, dehydration can best be appraised by continued evaluation of the history, the turgor of the skin, the resistance of the eyeballs, the state of the peripheral circulation, and the fluid intake and output. All of these factors must be considered together and should then be interpreted with the aid of available laboratory measurements. In severe dehydration, an excess of 10 per cent of the body weight may be lost as water. Hence, in a 70 kilogram dehydrated adult the water requirement might vary between a few hundred and seven thousand cubic centimeters. The clinical response to therapy is frequently the best indication of adequate water replacement.

Of equal importance with estimation of water loss are considerations of electrolyte losses and imbalance. Anion and cation losses from the body, especially sodium and chloride, rarely take place in quantities proportional to their concentrations in body fluids. The presence of acidosis or alkalosis depends then on whether the route of electrolyte removal favors acid or base deficit. In addition, acidosis may be augmented by retention of anions (for example, ketone bodies or phosphates). Alkalosis due to base retention is rarely seen unless sodium intake (as with sodium bicarbonate medication) has been excessive, and even then is usually associated with diminished renal function, or with a coincident loss of chloride and water through vomiting. Although definition of alkalosis or acidosis, and the degree of either, rests finally upon laboratory measurements of the blood, it is usually possible from the history and physical findings to decide which exists. A few laboratory determinations should then be sufficient to plan and carry through therapy.

The clinical conditions leading to metabolic acidosis or alkalosis are well known and have been described in detail elsewhere.<sup>1 4 5</sup> Three histories describing some current methods of dealing with acidosis or alkalosis will demonstrate general principles which can be applied to most such problems.

## REPAIR SOLUTIONS

The advantages of converting all electrolyte concentrations of the blood or of parenteral solutions to milliequivalents cannot be over emphasized. By so doing one can readily visualize in comparable and equivalent quantities electrolyte losses and replacements.<sup>1,4</sup> Four different solutions are graphically represented in terms of milliequivalents per liter in Figure 159. One of these solutions or combinations

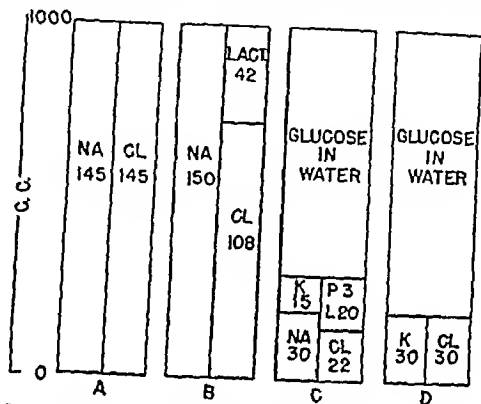


Fig. 159—Repair solutions used in metabolic acidosis and alkalosis. See text for discussion.

of them have been found to meet the needs of the vast majority of patients suffering from metabolic acidosis or alkalosis who require parenteral fluid therapy. The compositions of the fluids are:

**Solution A**—Isotonic saline containing 145 milliequivalents of sodium and of chloride per liter

Sodium chloride  
Distilled water

8.5 gm  
q.s. ad 1000.0 cc.

**Solution B**—An isotonic solution containing 150 milliequivalents of sodium, 108 milliequivalents of chloride and 42 milliequivalents of lactate per liter

Isotonic saline solution  
Sixth molar sodium lactate solution  
or

7.0 cc  
250 cc.

Sodium chloride  
Sodium lactate  
Distilled water

6.4 gm  
5.6 gm  
q.s. ad 1000.0 cc.

**Solution C** \*—Potassium ion solution containing 30 milliequivalents of sodium, 15 milliequivalents of potassium, 22 milliequivalents of chloride, 3 milliequivalents of phosphate, and 20 milliequivalents of lactate per liter. Note that total electrolyte concentration is hypotonic in respect to plasma, and hence glucose must be incorporated in it

Sodium lactate	2.21 gm
Potassium chloride	0.89 gm
Potassium phosphate	0.25 gm
Sodium chloride	0.58 gm
Glucose	50.0 gm
Distilled water	q.s. ad 1000.0 cc

**Solution D**—Strong potassium solution containing 30 milliequivalents per liter each of potassium and chloride, but also hypotonic unless glucose is incorporated

Potassium chloride	2.25 gm
Glucose	50.0 gm
Distilled water	q.s. ad 1000.0 cc.

Additional glucose can be incorporated in any of these solutions if they are to be given intravenously and if hypertonic solutions are not a disadvantage

### DIABETIC ACIDOSIS

**CASE I** †—An 18 year old juvenile diabetic volunteered to undergo a metabolic study. There was a control period of oral diet and 70 units of insulin per day, a period of oral diet without insulin, a period of parenteral therapy with an average of 180 units of insulin per day, and a final period of oral diet with an average of 75 units of insulin per day. Table I and Figures 160 and 161 present most of the salient features observed during the course of this study.

**Comment**—From Table I it is evident that during the oral diet, no insulin period the average oral intake of fluid exceeded urinary output by only about 100 cc a day. Allowing for an estimated daily loss of 900 cc of insensible water, there was a considerable negative water balance in spite of the good fluid intake. The reductions in serum carbon dioxide content, chloride, and sodium during insulin withdrawal, while definite and in the expected directions, were not very striking because in the interests of the patient the period of insulin withdrawal was terminated before nausea, vomiting, thirst, and starvation led to the same degree of dehydration and acidosis usually suffered in diabetic coma.

\* Designed by Dr. A. M. Butler

† Data from this patient have been previously published<sup>2</sup> and are reprinted here by permission of the American Association of Physicians

The repair solutions used were as follows. During the first hour 1 liter of solution B was given, during the remaining forty seven hours 6.7 liters of solution C containing in addition 30 gm of hydrolyzed casein. The average daily milliequivalents of electrolytes which these two solutions supplied are shown in Table I.

The electrolyte losses and replacements are best demonstrated by balances. Sodium and chloride are depicted in Figure 160 which is so

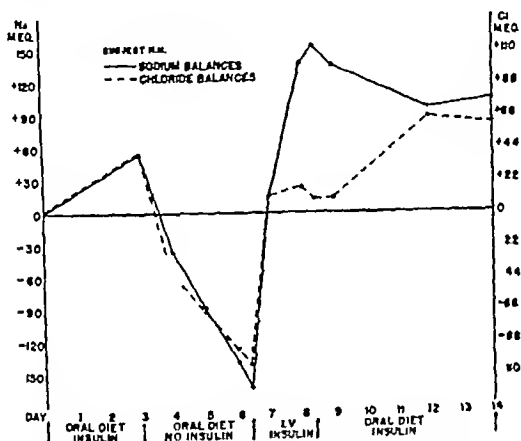


Fig 160—Sodium and chloride balances in patient with diabetic acidosis (Case 1) (Reproduced by permission of the American Association of Physicians)

constructed that 150 milliequivalents of sodium correspond to 110 milliequivalents of chloride. Thus during the no insulin period these ions were lost in approximately the proportions they were present in the extracellular fluid. The slight departure from this proportionate loss is reflected in the changes in serum concentrations of sodium and chloride and in carbon dioxide content. One liter of solution B replaced the losses sustained during the 3.4 days of insulin withdrawal and subsequent administration of the relatively small quantities of sodium and chloride present in solution C produced a definite retention of both ions. It should be emphasized that although the quantity of sodium and chloride administered to this patient was considerably less than is usually used in the treatment of diabetic acidosis it furnished almost double the actual quantities lost during

TABLE 1  
METABOLIC DATA FOR CASE I—DIABETIC ACIDOSIS

	Oral Diet Insulin	Intravenous Insulin	Oral Diet Insulin
Average total fluid per day (cc)	2500	3850	2020
Average parenteral fluid per day (cc)	0	3850	0
Average urine output per day (cc)	1550	2075	1170
Average fluid balance per day (cc)	+ 950	+ 1775	+ 850
Average intake per day (mEq ) Sodium Chloride Potassium	104 96 59	204 137 48	104 96 59
Serum concentration(mEq /liter) CO <sub>2</sub> , Chloride Sodium Potassium	32 101 143	23 104 138 44	31 102 140 49
Days	1	2	3

the insulin withdrawal period. Data not all presented here indicated that while most of the excess chloride given was excreted 95 per cent of the total sodium administered was retained and 35 per cent was retained in the cells.

Solution B appears to be better suited than isotonic saline for most conditions in which there is dehydration and acidosis for it supplies both sodium and chloride ions in the concentrations that are found in the plasma. The slight surplus of sodium ion serves to supply sodium which has been lost in excess of chloride through the kidneys without producing the hyperchloremia so frequently seen after infusion of isotonic saline. In our opinion, a solution similar to solution B should be administered parenterally in metabolic acidosis at a fairly rapid rate (6 to 8 cc. per minute if cardiac function is adequate) until the estimated extracellular water sodium and chloride deficits have been replenished. Estimates of total sodium and chloride losses in the most severe cases of diabetic acidosis do not exceed 35 to 40 grams of salt.<sup>1</sup> Four liters of solution B would meet such a loss and can be taken as the maximum quantity necessary in considering sodium and chloride replacement. Much less than this may suffice. Thereafter sodium and chloride are needed only in the quantities necessary to cover continuing losses. Such requirements excluding abnormal renal or extrarenal losses amount to 2 to 3 grams of salt daily (250 cc. to 350 cc. of isotonic saline solution). Balanced *hypotonic* solutions rather than isotonic solutions are in the opinion of one group preferable in all parenteral therapy.<sup>1</sup>

During the no insulin period there was a marked deficit of potassium the predominant intracellular cation (Fig. 161). The figure is so constructed that if potassium were depleted only as a result of protein breakdown the nitrogen and potassium data would fall along the same line. The striking loss of potassium in excess of that which can be accounted for by protein catabolism is apparent. Replacement of this excess potassium loss was only partially effected by the 6.7 liters of solution C administered during the 48 hour period of parenteral fluids.

In spite of the strongly negative potassium balance the serum levels of this ion were constant throughout the study except for one low value noted on the tenth day four days after insulin and active treatment had been reinstituted. However recent reports have demonstrated that serum potassium may fall to levels capable of producing serious symptoms during the treatment of diabetic acidosis with intravenous glucose solutions and large quantities of insulin although the serum level may be normal or even high before insulin and glucose



therapy.<sup>7,8</sup> Administration of potassium during the treatment of diabetic acidosis is then desirable for two reasons (1) to replace the intracellular quantities lost in excess of protein catabolism, and (2) to prevent hypopotassemia which accompanies therapy.

*It should be emphasized that because of the marked toxicity of potassium in high concentrations in the serum any parenteral administration of this ion must be carefully controlled.* In diabetic acidosis with the associated tissue depletion of potassium and the tendency

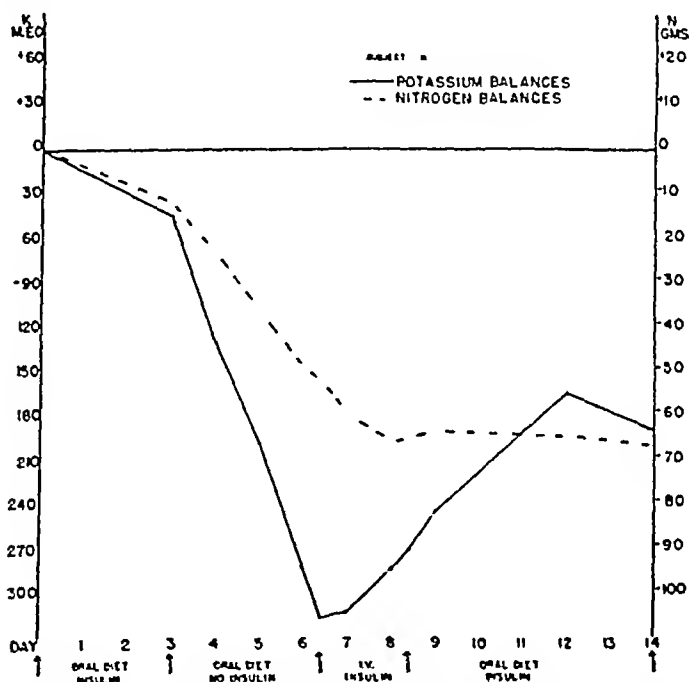


Fig 161—Potassium and nitrogen balances in patient with diabetic acidosis (Case I)

of serum potassium to fall during therapy, if urinary output remains adequate, a solution such as solution C (or possibly a somewhat stronger one relative to potassium) can in most instances be given with safety. For adults it should not be administered faster than 4 to 5 cc per minute. We have not exceeded a total daily quantity of four liters, or 60 milliequivalents of potassium. It is also our rule not to start potassium administration until treatment has been under way for three or four hours, after the major extracellular deficits have been replenished by the salt and lactate solution, and after the blood sugar has begun to fall with insulin treatment. Where possible oral administration of potassium as broth or as KCl in doses of 3 to 6 grams per

*day is preferable, especially if serum potassium measurements are not available*

In the patient here presented there was a negative phosphorus balance of 10 mg per kilogram over and above nitrogen loss. The occurrence of striking reduction in serum phosphorus during treatment of diabetic coma has been reported and the possible importance of phosphorus administration in such treatment has been recently stressed.<sup>12</sup> It is probable therefore that further experience will demonstrate the advisability of incorporating more phosphate than is present in solution C in treatment of this type of acidosis.

Some difference of opinion still exists as to the advisability of including glucose during the early hours of therapy of diabetic coma.<sup>14, 15</sup> There can be little argument that as soon as the blood sugar begins to fall glucose should be incorporated in repair solutions in order that continued removal of ketone bodies may be insured and hypoglycemia prevented.

#### RENAL ACIDOSIS

Dehydration and loss of electrolytes are common in patients with renal insufficiency. The electrolyte pattern is extremely variable but is usually that of acidosis due to impairment of base saving mechanisms of the kidneys. Retention of phosphate and sulfate frequently augments the acidosis. Chloride in addition to base also is usually lost in the urine. The almost invariable vomiting of uremia may further accentuate chloride deficit. Combinations of solution A and B and glucose in water judiciously used may aid in attempts to restore homeostasis. No rules in our experience can be laid down for estimating the quantity of each needed for an individual patient. Because of the ease with which edema is produced it is usually unwise to attempt completely to correct acidosis and chloride deficit as reflected by the serum carbon dioxide content and the serum chloride concentrations. What additional water is required should be supplied as glucose in water which serves in some cases as a diuretic; it also helps to supply caloric needs thus reducing endogenous protein catabolism. Because potassium retention is frequently present in uremia potassium solutions are contraindicated unless a specific need can be demonstrated by measurement of the concentration of this cation in the serum.

#### METABOLIC ALKALOSIS—MILD

CASE II—A 54 year old white man with a known duodenal ulcer of many years duration entered the hospital because of hematemesis. There was a history of excessive milk and alkali intake for years. A persistent anemia

had been present for about eighteen months. There was no clear cut history of antecedent nephritis but hypertension had been known to be present for about ten years. The hematemesis ceased before any shock developed and the patient did well until the ninth hospital day, when he became obstructed. After vomiting 1200 cc, constant gastric suction was started.

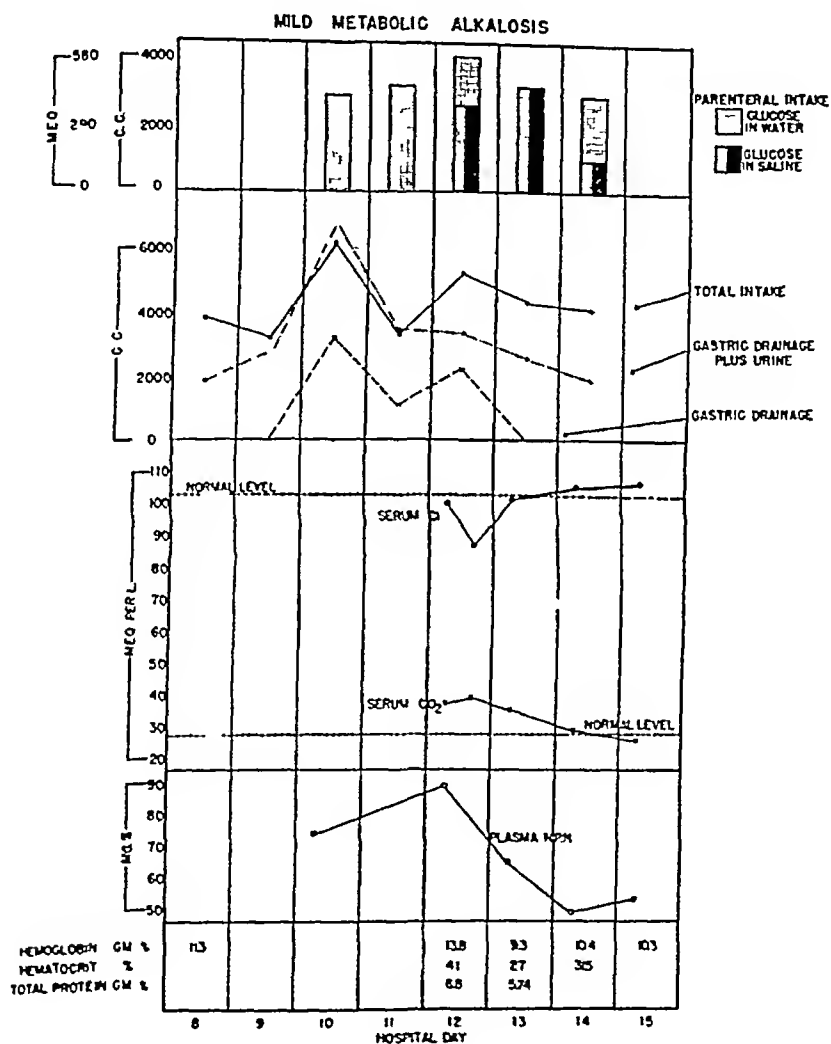


Fig 162—Patient with mild metabolic alkalosis (Case II)

The alkalosis which resulted and its repair are shown in Figure 162. Note (1) That on the ninth and tenth days only glucose and water were given to replace the urinary plus gastric fluid losses, (2) That although intake and measured fluid output practically balanced during these days, no allowances were made for losses from perspiration, through the feces, or for insensible

losses (3) That in spite of a good *water* intake and output, by the twelfth day he had a significant alkalosis (plasma carbon dioxide content 37 mEq per liter) hypochloremia (serum chloride 87 mEq per liter) increasing azotemia (plasma nonprotein nitrogen 89 mg per 100 cc.) and signs of dehydration (elevated hemoglobin hematocrit and serum protein) (4) That these changes were readily reversed by the administration of about 7 liters of saline on the twelfth and thirteenth days.

*Comment*—This patient illustrates several important points in the treatment of alkalosis of the type usually encountered namely that due to loss of gastric fluid During the first two days on gastric suction when he was receiving only glucose, his condition deteriorated because electrolyte losses were not replaced although fluid losses to some degree were covered The good response to isotonic saline demonstrates the well known suitability of this solution for the treatment of most such cases It should be emphasized that in alkalosis due to vomiting although chloride loss is primary sodium also is lost both in the gastric contents and in the urine, reflecting an attempt by the kidneys to compensate for the deficit of chloride<sup>16</sup> Hence isotonic saline, containing one third more chloride than is present in the plasma (115 milliequivalents of chloride per liter in isotonic saline and 100 milliequivalents per liter in plasma) provides a desirable excess of chloride ion In this case it was possible since the gastric losses were known to calculate at any point in his course approximately what the deficits were. Thus, between the ninth and eleventh day he lost approximately six and one half liters of gastric fluid The concentration of chloride in gastric fluid is considerably greater than that in the plasma<sup>16</sup> In this patient the gastric fluid contained 118 milliequivalents of chloride per liter The total chloride loss was therefore in the neighborhood of  $6.5 \times 118 = 767.0$  milliequivalents. Likewise the sodium loss must have been considerable from both the stomach and from excretion of the highly alkaline urine which he was forming Six liters of normal saline containing 870 mEq of both sodium and chloride ( $6 \times 145 = 870$ ) would provide adequate replacement of chloride and some excess of sodium Actually the losses were overestimated somewhat and he was given seven liters of isotonic saline, which probably furnishes an explanation for the slight hyperchloremia present on the thirteenth and fourteenth days The standard practice of replacing quantitatively gastric losses with normal saline is probably a safe one though undoubtedly many cases will receive too much salt under such a regimen If the kidneys are functioning properly and fluid intake is adequate the body can usually rid itself of the excess.

## METABOLIC ALKALOSIS—SEVERE

CASE III \*—A 58 year old white man was admitted for stupor of twelve hours' duration. From the family it was learned that for many years he had taken up to one pound of soda bicarbonate weekly for epigastric pain. For several months there had been progressive nausea and vomiting, loss of about 50 pounds, and restriction of diet practically to milk. During the two days prior to admission he had not voided and had become disoriented. There was no known previous kidney disease, but he had had nocturia for several years. On examination he was semicomatose and poorly nourished. There were signs of extreme dehydration and collapse. Blood pressure was 90/60, the pulse was weak, the extremities cold, the skin and tongue dry and the lips cyanotic.

Initial laboratory findings were Hematocrit 49 per cent, hemoglobin 17.5 gm., white blood count 15,600, blood nonprotein nitrogen 105 mg. per 100 cc., total protein 8.59 gm. per 100 cc., albumin 3.35 gm. per 100 cc., globulin 5.34 gm. per 100 cc., serum calcium 8.28 mg. per 100 cc., phosphorus 10.4 mg. per 100 cc., plasma carbon dioxide content 52 milliequivalents per liter, plasma chloride 40.2 milliequivalents per liter, serum sodium 115 milliequivalents per liter. Examination of the urine revealed a pH of 7.5, specific gravity of 1.018, a 2+ albumin, no sugar or acetone, 6 to 8 leukocytes and 3 to 5 erythrocytes per high power field.

Subsequent x-ray examinations established the presence of a duodenal ulcer with complete pyloric obstruction which was eventually relieved by gastrojejunostomy and vagotomy.

The salient features of his course and treatment are shown in Figure 163. Note first that in spite of a strongly positive fluid balance (over 14 liters) and tremendous quantities of sodium chloride (over 100 grams) during the first four days, his alkalosis remained essentially unchanged during this period. Beginning on the sixth day, coincident with a diuresis, and possibly with an increase in the quantity of potassium administered, his serum carbon dioxide content gradually fell, serum chlorides rose, and nonprotein nitrogen fell, until they reached essentially normal levels on the thirteenth day. Note also the initial low serum sodium rising to normal on the fifth day, and low serum potassium levels persisting until the ninth day.

*Comment*—The management of this patient was vastly more complicated than that of the former one. The marked alkalosis in this instance had almost surely been accentuated by the previous excessive intake of base. Severe dehydration with shock were pressing symptoms. These were vigorously treated with large quantities of isotonic saline and whole blood with relief of the shock and dehydration (he was in fact edematous by the fourth hospital day). In spite of this therapy the alkalosis was practically unchanged during the first four

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\* A more detailed account of this patient will be published later.



times be effected by administering 3 to 6 gm of KCl daily by mouth as soon as the obstruction is sufficiently relieved to allow fluid to pass into the duodenum

### SUMMARY

Choice of the types and quantities of parenteral solutions to be administered in the treatment of metabolic acidosis or alkalosis depends upon estimation of the total loss of body water and of the deficit of extracellular and intracellular electrolytes. No specified rules can be laid down for the replacement of these losses. One of the four solutions described above (or combinations of them) have been found to meet the needs of most cases. Which solution to use, and the quantity of each necessary, is best determined by an initial estimation of fluid and electrolyte needs, and subsequent frequent evaluation of the response of each individual patient.

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# A CASE OF RHEUMATIC HEART DISEASE WITH PERIODIC ARTERIAL EMBOLISM AMBULATORY TREATMENT WITH DICUMAROL

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One of the most serious complications of rheumatic mitral stenosis with auricular fibrillation is arterial embolism from mural thrombus of the left auricle. It is unpredictable in its occurrence and such an embolus may be carried to any artery in the body. A single embolus for example, may produce fatal ischemia if lodged in a cerebral vessel or multiple smaller emboli at varying intervals may obstruct the circulation to abdominal organs such as the kidney where they may produce cumulative renal damage and terminal uremia.

There has been no effective prophylaxis for this condition. Restoration of normal rhythm with quinidine has been attended at times by embolism when the auricle resumed contraction. However, not only is quinidine often unsuccessful in chronic mitral disease but the normal rhythm rarely persists if restored and the stenosis of the valve with consequent left auricular stasis may produce mural thrombosis even with normal rhythm.

The patient who is presented here, who is also the junior author (R. P. J.) was faced with the experience of repeated arterial embolism. He is a 38 year old organic chemist who has no history of rheumatic infection but who has known of his rheumatic heart disease since 1930. In 1934 he had an embolus to the spleen and five emboli since that time the last one in April 1947 lodging in the left femoral artery with successful embolectomy by Dr. Chester Brown.

Auricular fibrillation has probably been present for fifteen years but digitalis has been taken regularly only since an appendectomy in 1938.

At the time of the femoral embolectomy heparin was injected into the artery and was continued intravenously to a total of 2.2 gm. in five days. It was decided that it was justifiable to try the prolonged administration of dicumarol and this was started shortly thereafter.

Physical examination on April 21, 1947 showed no signs of congestive failure. The heart, especially the auricles, was seen to be extremely large on fluoroscopic examination. The auscultatory findings were those of mitral regurgitation and stenosis, and electrocardiogram showed auricular flutter.

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with varying block, the flutter rate being 480 and the ventricular rate averaging 80

Experience with prolonged use of dicumarol in ambulatory patients with mitral stenosis is as yet very limited. Dr. Irving Wright has reported on a small series. It has been given to patients with coronary occlusion, and following recovery to prevent repeated coronary thromboses. Dr. Sterling Nichol has described this procedure. Similarly dicumarol has been used to inhibit the repetition of pulmonary embolism from chronic phlebothrombosis in the legs.

In the case of our patient the circumstances are peculiarly favorable for close observation, in that his chemical knowledge and the immediate availability of his own laboratory make his experience of particular value.

We wish, therefore, to present his history in his own words.

At roughly two year intervals during the past twelve years, I have experienced embolic phenomena, two or three of which were diagnosed as involving the spleen. These varied somewhat in the intensity and duration of the discomfort with which they were associated. They were characterized by more or less severe pain in the lower left side or upper abdomen or both, usually lasting for several hours and followed by a few days of slightly elevated temperature.

The most recent attack, occurring in April of this year, was considerably more dramatic than its predecessors and caused me to realize the potentially serious crippling action of an embolus.

I was sitting at my desk, collecting a few thoughts preparatory to a conference in the Director's office, when my left leg began to feel as though it were "going to sleep" and I did the usual stamping and kicking in an attempt to promote better circulation. In the middle of my conference, the sensations increased in intensity so that I could not sit still and soon the whole leg became painful and pallid.

My physician was summoned and, being familiar with my heart condition, he quickly surmised the state of affairs and made arrangements for a surgeon and hospital services.

Within a period of a few hours from the time the obstruction had first interfered with blood supply to my leg, the surgeon and my physician were removing a well fibrinated clot nearly one centimeter in diameter from the bifurcation of the left femoral artery.

Recovery was uneventful except for what appeared to be a sympathetic reaction which so constricted the blood vessels in my right leg that there was an insufficient blood supply to the calf and foot. Neither sympathetic nerve block nor papaverine therapy provided any permanent improvement, but during a period of several weeks (aided perhaps by my cutting down on my use of tobacco) normal circulation returned to the right leg as well.

After my release from the hospital a course of heparin injections was started 2.15 gm of the sodium salt being administered during five days time. No clotting times were run.

Following the use of heparin both Dr Carr and Dr Sprague suggested that I continue anticoagulant therapy using dicumarol and in preparation for this we collected data on administration prothrombin determination and thromboplastin preparation with the plan that I would conduct the tests necessary to follow my own prothrombin level.

Dr Goodale of the Worcester City Hospital was most helpful in describing their prothrombin test method and thromboplastin preparation. Miss Land

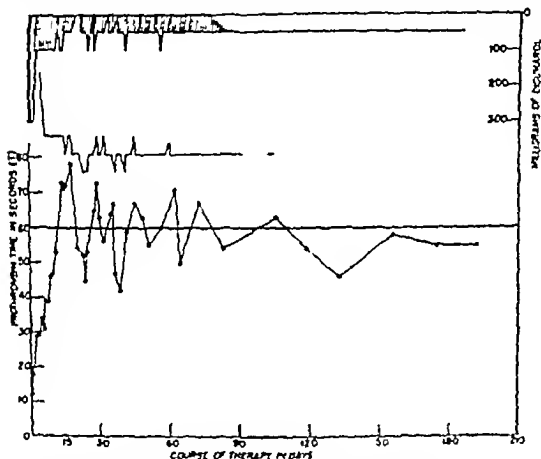


Fig 161—Dosage of dicumarol and prothrombin times. The center curve is the reciprocal of the upper dosage line and is superimposed to indicate more clearly the dosage response relationship.

wehr, a member of our own Foundation staff with some experience in prothrombin studies helped me with the initial determinations. The test method used is that of Quick without refinements as suggested by Shapiro and others. It was found desirable to prepare the thromboplastin from fresh rabbit brain. The brain powder is stored over a drying agent in a desiccator maintained below 10 C. In the initial testing two normals were used as controls, one with a prothrombin time of 12 and the other 15 to 16 seconds.

Dicumarol administration (Fig 161) was begun in the usual manner—300 mg, the first day, 200 the next and 100 thereafter. By this procedure the prothrombin time was carried to too high a value and I subsequently discovered that the sixty second level maintenance dose in my case is only

about 50 instead of 100 mg per day. Determinations were made every day for eleven days, then a day or two was skipped at intervals. Later the period between tests was increased to one week, then two or three weeks. At present the determinations are made at monthly intervals.

Here the test results are charted over the period of therapy in days. Some irregularity in the values obtained during the first month or two may have been caused in part by trying to employ the 100 mg dosage level when only 50 mg were required. This may be demonstrated by comparing this section of the dosage chart with the prothrombin times, a rough dosage response

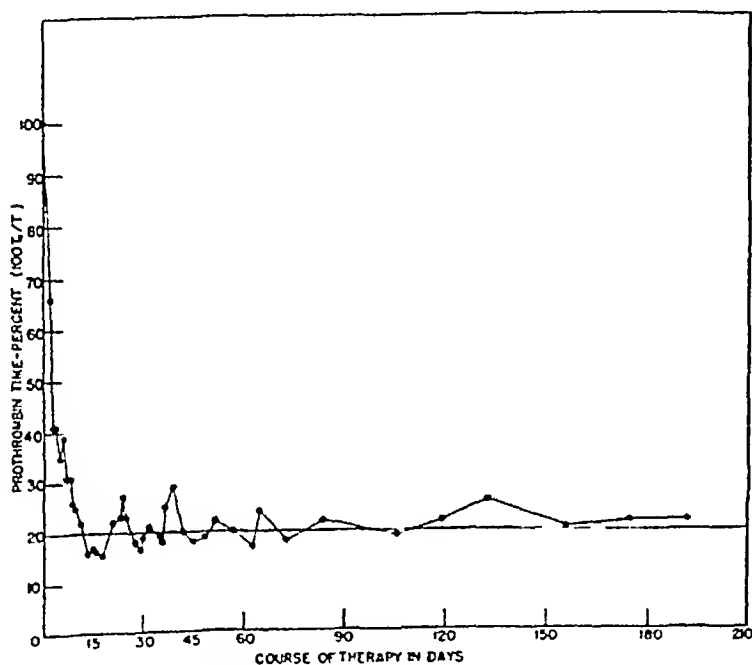


Fig 165—Prothrombin time per cent showing stabilization at a dose of 50 mg of dicumarol daily

relation is at once apparent. I think that some of this irregularity might have been avoided and a smoother transition from 300 mg to 50 mg made after seven or eight 100 mg daily portions. This would have constituted a total of nine or ten days time in reaching the desired prothrombin level. This "60 second" line is arbitrarily chosen for reference. Actually with 50 mg of dicumarol per day the average time value seems to be a little less than sixty seconds.

In Fig 165 the prothrombin time per cent is similarly charted. This time per cent is 100 times the ratio of the normal to the measured prothrombin time, and as I was a little confused to learn, bears no simple relation to the actual plasma prothrombin concentration. As can be seen, the 50 mg dosage level in my case seems to maintain the prothrombin time per cent a little

above 20 (this is the 20 per cent reference line) a value which should be low enough to prevent clot formation and growth in the auricular cavity

In this portion of the chart when the maintenance dosage level was uncertain the per cent value fell to 15 (that is, the prothrombin time rose to nearly 80 seconds) and the first symptom of overdosage was encountered. On a few occasions during this period usually while I was bending over a few drops of blood flowed from my left nasal passage. On these days I centrifuged a sample of my urine but was unable to detect any red cells in the sediment. No other side effects of the dicumarol therapy have been observed.

A report on March 22, 1918 shows this patient to be still in good condition, but he has made the observation that it was necessary to reduce his weekly dosage of dicumarol during the winter months from 350 to 200 to 300 mg because of the tendency for the prothrombin time to rise during a respiratory infection. In November he had a cold for which he took sulfadiazine for three days. Two days after that it was found that the prothrombin time was 100 seconds and dicumarol was omitted for two days after which the prothrombin time fell to 40 seconds and the dosage was resumed at 50 mg a day.

#### SUMMARY

This case report is submitted in the hope that it will aid in the management of similar patients. It is appreciated that it is an uncontrolled experiment and that the effectiveness of the therapy in preventing embolism is unproved. However we wish to emphasize these points based on the continuous administration of dicumarol over a period of eight months without untoward effects \*

1. Dicumarol is a drug which it is practical to give as a daily medication to a young ambulatory patient with mitral stenosis and multiple recurrent arterial embolism.

2. Very close laboratory control by a single expert technician is recommended during the dosage determination period.

3. After the daily dose is standardized which in this case is 50 mg prothrombin determinations may not be necessary oftener than once a month.

4. A prothrombin time of 50 to 60 seconds is well tolerated. Slight nasal bleeding has been used as a sign of overdosage when the prothrombin time was nearly 80 seconds (15 per cent prothrombin time).

5. In a small group of similar cases where careful control is possible this procedure of dicumarol maintenance may be valuable in the prevention of arterial embolism.

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\* This is now fifteen months (July 1918)



## THE MEDICAL MANAGEMENT OF PATIENTS WITH URINARY CALCULI

HOWARD I. SURY, M.D.\*

The proper care of patients with urinary calculi is a more complicated problem than was once believed. With the advent of cystoscopy and x-ray the diagnosis of presence, position and size of most stones has been greatly facilitated. In like manner much evidence regarding the amount of obstruction to and the function of the kidneys has been made available through the use of cystoscopy and pyelograms. Urinary stones, however, are not all radiopaque and it is occasionally with the greatest difficulty that the proper diagnosis is made, even with our modern techniques.

Although the scope of this paper is confined primarily to the medical management of patients with urinary calculi, a few thoughts regarding surgical management are briefly presented. Surgery for urinary calculi is much less an emergency procedure today than it was a few years ago. With the availability and use of our chemotherapeutic and antibiotic agents today, a patient with urinary stones may be rightfully treated more conservatively than in the days before their use. In other words, temporizing with a small ureteral stone in an attempt to allow the patient to pass it—or in several attempts to extract it cystoscopically—may now be a relatively safe procedure whereas a few years ago it might well have been a lethal procedure. Conservatism still does have its limitations, however. The amount of pain the patient has, the size and location of the stone, the response of infection (if present) to chemotherapy, the degree and duration of obstruction—these factors must be weighed carefully by the attending urologist in making decision as to proper surgical management. Availability to a qualified medical center is also a factor and this was one reason why either prompt surgery or transfer to a zone where proper care was constantly available had to be advised in overseas army installations.

Why do certain people have kidney stones? Here is where the problem becomes a bit more complicated. One proper answer could be—because they do not drink enough water. A huge fluid intake—actually a huge fluid output—this is the nearest least common denominator for the prevention of all types of urinary stones. The problem of pro-

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lithiasis is complicated because there are many different chemical types of stones, and what form of therapy is beneficial for patients with one type of stone may be harmful to a patient with another type of stone. Fuller Albright<sup>1</sup> neatly based his discussion of treatment of urinary stones on one major premise and its corollary.

*Premise* A patient with urine of such composition that some crystalloid precipitates out of it is predisposed to the formation of a stone composed largely of the precipitated crystalloid (compare cystine stones in cystinuria, uric acid stones in gout, and calcium phosphate or calcium oxalate stones in hyperparathyroidism).

*Corollary* In a case in which there is a tendency for stones composed predominantly of a certain crystalloid to form, treatment should be directed to altering the composition of the urine in such a way that solution of the crystalloid is favored.

The following discussion will attempt to present each chemical type of stone from that point of view. In other words, in treating each of the major types, important factors regarding the etiology, diagnosis and practical therapy will be considered. There are four prevalent major types of urinary calculi. There are a few less prevalent types. Some patients have stones which are mixtures of two or more types.

The four prevalent major types of urinary calculi are

- 1 Cystine stone
- 2 Uric acid stones
- 3 Calcium oxalate stones
- 4 Calcium phosphate (with or without calcium carbonate and magnesium ammonium phosphate) stones

### CYSTINE STONES

Although cystine stones are relatively rare, they should always be considered in a patient with kidney stones, and evidence for or against their probability should be obtained in a diagnostic "stone work up." Cystine stones are the result of crystalloid precipitation of cystine in patients with cystinuria. This latter condition is usually a familial disease and may or may not be associated with actual stone formation. A carefully taken family history, however, may frequently point the way to the tentative diagnosis of cystine urolithiasis. The cause of cystinuria, although not completely understood, is some form of faulty protein metabolism. Cystine stones can be of any size and are usually found in patients passing an acid urine. They are radiopaque, having a rather characteristic waxy appearance and occasionally showing a melding of small stones into large stones. The diagnosis can usually be confirmed by a careful examination of the urine sediment. The char-

acteristic hexagonal cystine crystals can be easily seen under the microscope. To confirm the diagnosis, the following simple chemical test can be done on a sample of the first morning urine

To 5 cc. of urine made alkaline with ammonium hydroxide 2 cc. of 5 per cent sodium cyanide solution is added and allowed to stand for from five to ten minutes a few drops of a freshly prepared 5 per cent sodium nitroprusside solution is then added in the presence of cystine a permanent deep purplish red will develop

As has been stated most patients with cystine stones pass an acid urine and since cystine is soluble in alkaline solutions some patients have been able to dissolve their renal calculi by taking alkalis by mouth thus forming an alkaline urine. One satisfactory regimen which is advisable for this type of case is an alkaline ash diet. Even more preferable, however is the use of sodium citrate 3 gm. three or four times a day and a normal diet. The voided urine should be examined by the patient after each voiding to verify the fact that ample alkalinity (7.0-7.5 by Squibb's nitrazine paper) is being maintained

Unfortunately the above regimen does not always work and it becomes necessary to treat the stone by some other method. In our laboratory in vitro experiments have shown that most cystine stones can be dissolved in a borate buffered solution (pH 8.0-9.0) or in a sodium bicarbonate solution. Retrograde dissolution of this type of stone has not been attempted by us as yet however. Surgery in some cases may be the treatment of disease.

### URIC ACID STONES

Uric acid stones usually occur in patients with an increase of uric acid in the urine. Consequently they are frequently seen in patients with gout. Patients with uric acid stones (or stones with uric acid and urate) comprise approximately 10 per cent of all cases of urinary calculi. Uric acid is precipitated in an acid medium and consequently patients with this type of stone usually pass an acid urine. Uric acid stones are not radiopaque and their diagnosis in some patients is quite difficult. It can often however be made by the x-ray proof of obstruction due to no cause visible by x-ray and in acid urine loaded with golden crystals of uric acid (or urates). Occasionally large filling defects in the kidney pelvis ureter or bladder suggestive of tumor are proved at operation to be uric acid stones. An old but still practical method of proving the presence of a nonradiopaque ureteral stone is the passage of a waxed bulb up the ureter and examining it thereafter for scratches made by the stone. This diagnostic procedure is helpful in differentiating the presence of stone or obstruction due to a lesion

other than stone, i.e., tumor. Patients in whom uric acid calculi are suspected should have blood uric acid determinations made. Elevation above the 2 to 5 mg. normal limits should be considered contributory evidence of abnormally high uric acid excretion and of the presence of uric acid stone.

While uric acid stones may be large or small, it should be remembered that renal colic can often be caused by showers of uric acid crystals coming down the ureter causing intermittent ureteral obstruction.

Uric acid and urate stones, though somewhat soluble in alkaline solutions, are usually less easily dissolved by alkaline solutions (borate buffer at pH 8-9 or sodium bicarbonate solutions) than the cystine stones. Warm solutions of sodium bicarbonate (the heat makes the solution more alkaline) have been used, however, to dissolve uric acid crystals *in vitro* and in patients with partially blocked ureters due to uric acid crystals. Good medical management of these patients should be directed to prophylactic treatment which again consists in the use of a regimen which will promote an alkaline urine (using sodium citrate 3 gm. three or four times a day and measuring the urine pH by Squibb's nitrazine paper to verify the fact that alkalinity [pH 7.0-7.5] is being maintained). These patients should also be placed on a low purine diet, which can be planned from the following chart.

### LOW PURINE DIET

#### FOODS ALLOWED

*Soups* Cream soups made with any of the following vegetables

#### *Vegetables*

Beets	Okra
Broccoli	Potatoes white
Brussels sprouts	Potatoes sweet
Cabbage	Pumpkins
Carrots	Rutabagas
Celery	String beans
Corn	Tomatoes
Cucumbers	Turnips
Dandelion greens	Eggplant
Lettuce	

#### *dairy Products*

Cream	Cheese cottage cream and Swiss
Milk	Eggs
Butter	

#### *ereal*

Cream of wheat	Cornflakes
Hominy grits	Noodles
Rice	Macaroni
Farina	

*Breads*White bread  
Biscuits

Crackers

*Butter and All Fats**Beverages*Unfermented fruit juices  
MilkWater  
Postum*Nuts*Almonds  
Hazelnuts

Walnuts

*Fruits* All kinds.*Desserts* All simple desserts such as bread puddings, cornstarch pudding, ice cream, plain cake, etc.*Meats and Fish* Use occasionallyChicken  
Bacon  
LambOyster  
Crab  
LobsterFresh salmon  
Whitefish  
Haddock

## FOODS TO BE AVOIDED

*Meats and Fish*Sweetbreads  
Liver  
Brain  
Beef  
VealPerch  
Sardines  
Sausage  
Anchovy  
TurkeyLark  
Kidney  
Pike  
Goose*Beverages*Coffee  
TeaCocoa  
Alcohol*Vegetables*Asparagus  
Cauliflower  
Lentils  
MushroomsPeas  
Spinach  
Onions  
WatercressRadishes  
Lima beans  
Navy beans  
Kidney beans*Cereals* Oatmeal and all whole grain breads and cereals*Miscellaneous* Condiments, both gravies made from meat, foods difficult to digest, concentrated sweets, rich pastures and fried foods

## CALCIUM OXALATE STONES

Calcium oxalate stones comprise approximately 40 per cent of all urinary calculi and this chemical type is the most common primary stone (i.e. the first stone). These oxalate stones are often encountered in patients with increased oxalate excretion (oxaluria). Oxaluria (hyperoxaluria) may be due to (1) large ingestion of fe

with high oxalate content and "spillage" of oxalates into the urine—exogenous oxaluria, or to (2) a disturbance of the patient's metabolism in which large amounts of oxalates are excreted in the urine though the oxalate intake is not excessive (endogenous oxaluria). Calcium oxalate stones, however, are also frequently seen in patients without hyperoxaluria. Conversely, patients with hyperoxaluria and no oxalate stones are frequently seen. Calcium oxalate stones may also be found in patients with hyperparathyroidism. These calculi are hard, usually single, small to medium sized, radiopaque, and have sharp

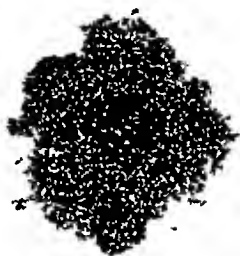


Fig. 166—X-ray appearance of a typical calcium oxalate stone. Note the spicules giving a characteristic snowflake appearance.

spicules giving the characteristic X-ray picture of a "snowflake" (Fig. 166) and appearing grossly as the typical "mulberry stone."

The diagnosis of an oxalate stone can often be made from the circumstantial evidence, i.e., a small stone with typical X-ray appearance, and urinary sediment loaded with oxalate crystals. All of these clues, however, may not be present. As to the medical treatment of a patient with a calcium oxalate stone, little can be done except to advise a high fluid intake (15 to 20 glasses of fluid daily) to help him to pass the stone spontaneously. Calcium oxalate precipitates in both acid and alkaline urines, consequently, the provision of a regimen most beneficial to a patient with this type of stone is difficult since neither acid nor alkaline therapy is indicated. The treatment often must be instituted by the urologist. Prophylactic treatment in these patients should consist

in (1) maintaining a large urinary output (patients should drink 15 to 20 glasses of fluid daily) and (2) avoiding foods with a high content of calcium and oxalate

Following is a chart showing the oxalic acid content of foods

*Food of High Oxalic Acid Content 0.1 per cent or Over to Be Avoided*

Beet tops	Cocoa
Chard (Swiss)	Dried figs
Chenopodium	Ground peppers
Parsley	Sorrel
Purslane	Black tea
Rhubarb	Chocolate
Spinach	Gelatin

*Foods of Moderate to Low Oxalic Acid Content 0.02 per cent and Over to Be Eaten Sparingly*

Beans green and wax	Strawberries
Carrots	Currants red
Celery	Concord grapes
Dandelions	Lemon peel
Endive	Lime peel
Okra	Oranges
Onions green	Coffee roasted
Peppers green	Tomatoes
Sweet potatoes	Rutabagas
Blackberries	Broccoli
Gooseberries	Brussels sprouts
Raspberries black	

*Foods Which Contain No Oxalic Acid*

Sugars	Peeled turnips
Fats	Sweet cherries
Starches	Seedless grapes
Cauliflower	Grapfruit
Water cress	Lemon juice
Cucumbers	Lime juice
Radishes	Mangoes
Peas	Melons
Apples	Nectarines
Avocados	Green gage plums
Green squash	

### CALCIUM PHOSPHATE STONES

Calcium phosphate stones (with or without calcium carbonate and magnesium ammonium phosphate) are statistically the most prevalent stones. They comprise about 40 to 45 per cent of all types of stone and about 80 to 90 per cent of recurrent stones. Their prevalence however is getting less due to the better control of urinary infections with modern chemotherapy. Since calcium phosphate precipitates in alkaline urine this type of stone is frequently found in patients who are taking large amounts of alkalis and in patients with hypercalcaemia and

hyperphosphaturia. Specifically, this is the type of stone which one encounters in 60 to 70 per cent of patients with hyperparathyroidism (calcium oxalate stones also occasionally occur in this disease). As to the percentage of calcium phosphate stones caused by hyperparathyroidism, however, it is low, probably well below 5 per cent. Diets containing large amounts of calcium, phosphate and alkali can in certain people cause calcium phosphate urinary calculi; consequently, it is not uncommon to find ulcer patients who are on a "Sippy regimen" entering the hospital with renal colic due to large or small kidney stones composed of calcium phosphate. Fruit and vegetable diets are alkaline ash diets, and whereas herbivorous animals pass an alkaline urine, they do not have urinary calculi. That is because phosphate is excreted by their gastrointestinal tract and not in the urine. In man, however, phosphate is excreted in the urine, predisposing him to the possibility of forming calcium phosphate stones. One of the most common causes of calcium phosphate stones (in this group of cases, there is also much magnesium-ammonium phosphate) is urinary infection due to organisms which possess the power to split urea, form ammonia, and thus alkalize the urine. The *B. proteus*, *B. pyocyaneus*, certain strains of *Staphylococcus albus*, and some forms of enterococci are the most important urea splitting organisms. Infection of the urine with one of these bacteria, often introduced by urological instrumentation or surgery, is the most important cause of recurrent stones. Avitaminosis (low vitamin A intake) has been shown to be a contributing factor in the production of calcium phosphate stones. In some cases, both in experimental animals and in human beings, urinary infection precedes the stone formation while in others the stones form in kidneys producing apparently sterile urine. Another etiological factor of considerable importance in calcium phosphate stones is prolonged immobilization or bed rest. The lack of stress and strain on the bones of patients who are immobilized for long periods of time (fractured spines, paraplegics, and similar conditions) leads to decalcification of the bones with resultant high urinary calcium excretion and stone formation. Stasis, of course, due to obstruction at any part of the urinary tract is another factor and is an important contributing cause to all types of urinary stones.

As to the diagnosis, calcium phosphate stones may be of any size and are the most frequent chemical type found in large staghorn calculi. They are radiopaque, being either homogeneous or laminated due to increase in size of the stone by the formation of layer after layer of crystalloid (Fig 167). This type of stone is usually encountered in patients with alkaline or neutral urines and is the type asso-

ciated with urea splitting urinary infections and with hyperparathyroidism. Consequently in the stone work up blood calcium blood phosphorus and blood alkaline phosphatase determinations should be made. A twenty four hour sample of urine should be analyzed for total calcium and the urine should be cultured.

The surgical management of patients with this type of stone follows the general urological principles applicable to the treatment of all types of urinary calculi. It is noteworthy however that surgery



Fig. 167—X ray appearance of a typical phosphate stone. Note the laminated structure of the stone.

does have definite shortcomings in the management of recurrent stones. Unless each minute particle of stone is removed at the secondary operation (and this is frequently impossible) the remaining particle may act as a nidus for further stone formation and as a foreign body in the kidney making it impossible to completely or to permanently sterilize the urine. Some of the most difficult patients of this type may manufacture a stone every two to six weeks. These problems have inspired many to attempt other methods of management.

In patients with urinary infections, chemotherapy should be given in an attempt to sterilize the urine. It will often be found however that it is impossible to permanently sterilize the urine until all the



stone has been either passed or removed Sulfadiazine in small doses (0.5 gm four times daily) will often control a *B. coli* infection or a staphylococcal infection of the urine Mandelamine (methenamine mandelate), 2 or 3 tablets four times daily, may be used in patients who are sensitive to sulfa drugs To combat resistant gram positive organisms, penicillin may be given either intramuscularly or by mouth Streptomycin is very valuable in its effect against resistant gram negative organisms but should be given along with a urinary alkalinizer such as sodium citrate 2 gm five times daily

In patients with increased urinary calcium excretion (over 200 mg per twenty-four hours) or with persistently high blood calcium determinations and low blood phosphorus determinations, hyperparathyroidism should be suspected and exploration of the neck for hyperplasia or adenoma of the parathyroids should be advised In these cases, it is often best to operate on the parathyroids before starting other treatment for the stones

There are several medical regimens which may be of help in the management of patients with calcium phosphate stones The acid ash diet of Higgins<sup>2</sup> is one logical approach to the problem Its object is to promote a urine which will be acid and which will render calcium phosphate more soluble From the following chart, such a diet can be selected

### ACID ASH DIET

#### A ACID ASH FOODS

##### I Cereal—any one of the following servings

Cornflakes	1 cup heaping
Cornmeal (cooked)	$\frac{2}{3}$ cup
Farina (cooked)	$\frac{2}{3}$ cup
Oatmeal (cooked)	$\frac{1}{2}$ cup
Puffed wheat	1 cup scant
Puffed rice	1 cup heaping
Rice (cooked)	$\frac{1}{2}$ cup scant
Shredded wheat	$\frac{1}{2}$ biscuit

##### II Meat—any two of the following measured servings

Beef loin medium fat	4 by $4\frac{1}{4}$ by $\frac{1}{2}$ in
Chicken, broiler	one half
Chicken stewed	breast or thigh plus leg
Cheese Cheddar	$3\frac{1}{2}$ by 2 by 1 in
Codfish fresh cooked	$\frac{1}{4}$ cup
Frankfurters, large	2
Halibut	4 by 2 by 1 in
Ham, fresh	$4\frac{1}{2}$ by 3 by $\frac{1}{4}$ in
Heart beef	$2\frac{1}{2}$ by 3 by 1 in
Kidney, veal	$\frac{3}{4}$ cup
Lamb chop	3 med size
Lamb roast	5 by 5 by $\frac{1}{4}$ in

Liver beef	3 by 6¼ by 1½ in
Mackerel fresh	2 by 4 by 1 in
Oysters very large	3
Pork chop thick	1
Salmon fresh	3 by 4 by ¾
Salmon canned	½ cup packed
Trout	2½ by 3 by 1 in
Turkey 2 slices	2 by 3 by ¼ in
Veal chop	1
Veal roast	3 by 2 in
White fish	2¼ by 3 by 1 in.

III *Bread*—whole wheat—5 slices

IV *Eggs*—two

V *Miscellaneous*—any one of the following measured servings

Macaroni	¾ cup
Spaghetti	½ cup
Rice	½ cup
Corn	½ cup
Plain cake	1¾ by 1½ by 1¼ in

VI *Miscellaneous*—to be taken or not as desired

Cranberries  
Flour  
Plain cookies  
Pastry with custard  
Popcorn

## B. ALKALINE ASH FOODS

I *Cream*—¾ cup

II *Fruits and Vegetables*

Fruits and vegetables shall be chosen from the following list only. Any combination of fruits and vegetables may be selected but the total excess basic ash in the selected combination must not exceed 25 cc. daily.

Fruits	Amount	Cc. of Excess Basic Ash
Watermelon	2½ by 2½ by 1½ in	27
Grapes	½ cup or 21 grapes	27
Pear	1 medium	36
Apple	1 small	37
Grape juice	½ cup	39
Lemon juice	¼ cup	41
Cherry juice	¼ cup	44
Orange juice	¼ cup	45
Raspberry juice	¼ cup	49
Peach	1 medium	50
Lemon	1 medium	
Banana	¾ cup or 1½ large	56
Orange	1 medium	56
Cherries	¾ cup	61
Apricots	2 medium	62
Pineapple	½ cup diced	68
Muskmelon	¼ cup	75
Rhubarb	1 cup	86

*Vegetables*

Asparagus	½ cup	08
Green peas	¾ cup	13
Onions	½ cup	15
Pumpkin	½ cup cooked	15
Turnips	½ cup cooked	27
Squash	½ cup mashed	28
Radishes	10	29
Mushrooms	½ cup canned	40
Cauliflower	¾ cup cooked	53
String beans	¾ cup cooked	51
Tomatoes	½ cup	56
Cabbage	¾ cup cooked 1½ row	60
Tomato juice	½ cup	62
Sweet potato	½ medium size	67
White potato	1 potato 2½ in diameter	70
Lettuce	¼ head or 16 leaves	71
Celery	4 stalks or ¾ cup	78
Cucumber	⅓ cup sliced	79
Rutabagas	½ cup mashed	85
Carrots	⅝ cup	108
Beets	¾ cup	109

*Note* A few samples of permitted fruit and vegetable combinations are

Orange juice ½ cup	45	Apple 1	37
Grapes 16	27	Pineapple 2¼ cup	68
Cauliflower ¾ cup	53	Pears ¾ cup	13
Tomato ½ cup	56	Cabbage ½ cup row	60
Potato, 1 medium	70	Potato 1	70
	<u>251</u>		<u>218</u>

Muskmelon	75
Applesauce 1 apple	37
Tomato ½ cup	56
Asparagus ½ cup	08
Lettuce ¼ head	74
	<u>250</u>

If patient takes over 25 cc. excess base he should take one 5 gram ammonium chloride tablet for each excess of 6 cc.

## III To be omitted entirely

Almonds	Olives
Beet greens	Parsnips
Dandelion greens	Raisins
Figs	Spinach
Molasses	Dried fruits and vegetables

## IV Milk—1 pint

Where the diet is being prescribed for kidney stones milk as a beverage should usually be entirely omitted because of the high calcium and phosphorus content. The same is true of cheese.

## C NEUTRAL ASH FOODS

Butter	Lard
Candy—no chocolate bars	Olive oil
Cornstarch	Salad oil

Mayonnaise  
Sugar  
Taploca

Tea  
Coffee or Kaffee Hag  
Postum

## HIGH VITAMIN ACID ASH DIET

## Suggested Plan of Menu

## Sample Menu

*Breakfast*

Fruit  
Cereal and wheat germ  
Eggs  
Whole wheat bread  
Salt free butter  
Beverage  
Cream  
Sugar

Orange juice— $\frac{1}{2}$  cup  
Oatmeal— $\frac{1}{2}$  cup with 2 lb wheat germ  
Eggs—2  
Whole wheat toast—2 slices

Coffee or tea  
Steamed rice— $\frac{1}{2}$  cup  
Sugar

*Luncheon*

Meat  
Rice or substitute (see miscellaneous)  
Vegetable or salad  
Whole wheat bread  
Salt free butter  
Fruit  
Milk

Veal chop—1  
Steamed rice— $\frac{1}{2}$  cup  
Sliced tomatoes— $\frac{1}{2}$  cup  
Whole wheat bread—1 $\frac{1}{2}$  slices  
Salt free butter  
Baked apple—1 small  
Milk—1 glass

*Dinner*

Meat  
Two vegetables  
(cooked or raw)  
Whole wheat bread  
Salt free butter  
Dessert  
Milk

Roast beef (see list)  
Hubbard squash— $\frac{1}{2}$  cup  
String beans— $\frac{1}{2}$  cup  
Whole wheat bread—1 $\frac{1}{2}$  slices  
Salt free butter  
Taploca cream pudding  
Milk—1 glass

A regimen using urinary acidifiers such as ammonium chloride (15 grains four to six times a day) has the same purpose as the acid ash diet. These acidifying regimens are usually of definite benefit in preventing further stone formation (and of occasional benefit in dissolving soft stones) but they have the following drawback. The more acid the urine is made, the more calcium and the more phosphate is pulled out of the bones and pushed into the urine. Consequently the acidity of the urine in itself often cannot dissolve the stone because there is so much calcium and phosphate already present in the urine. Further more unless the urine is checked carefully with nitrazine paper and found to be acid pH 5.0 to 5.5 much harm may be done. This is true in patients with urea-splitting infections whose urines may remain alkaline due to the presence of the bacteria in spite of acidifying regimens. If these patients are given ammonium chloride more calcium and phosphate is excreted in the urine and growth of the stones may actually be enhanced.

Many other theoretically sound regimens aimed at dissolving calcium phosphate stones may have been suggested. Shorr<sup>3</sup> has pointed out the theoretical usefulness of estrogens and aluminum hydroxide gels in such patients. Estrogens have the effect of increasing the urinary output of citric acid. This urinary citric acid combines with the calcium ions participating in the precipitation of calcium phosphate, forming a soluble calcium citrate complex. The aluminum hydroxide gels (such as Amphojel) divert the phosphate excretion from the urinary tract to the intestinal tract, thus causing a lower phosphate concentration in the urine. The program is theoretically sound. For optimum results the accompanying diet is recommended.

With this diet 30 to 40 cc. of amphojel is given one hour after each meal and before retiring (four times a day). The total daily dose, therefore, is 120 to 160 cc. Constipation, which is the only likely complication, can be controlled by cascara, mineral oil, or milk of magnesia without interfering with the good effects of the regimen.

The recommended estrogen dosage in men is estrone sulfate (premarin) 1 or 2 tablets (1.25 mg. each) four times a day. For women, one tablet of estrone can be given four times daily for three weeks. A ten day pause to permit regression of the endometrium should then be allowed before resuming the estrogen.

This regimen, although sound theoretically, may or may not be of practical importance. It has not been used on sufficient patients to permit an accurate conclusion at the present time. The chances are, however, that the ammunition is not quite powerful enough.

The possibility of dissolving encrustations and stones composed of calcium phosphate has been recognized for many years. Phosphoric acid, acetic acid and other organic acids have been used by many urologists as bladder "washes" and irrigants for encrusted nephrostomy tubes. Citric acid, however, has both the advantage of acidity and the advantage of a special action on calcium which makes its use theoretically much more feasible. As was mentioned before, citrate combines with calcium ions, forming a soluble calcium citrate complex. In 1939, Albright, Sulkowitch, and Chute<sup>4</sup> reported the case of a hemiplegic and paraplegic with bladder stones which were dissolved by irrigating the bladder with a citric acid solution at pH of 4. Not only were the stones dissolved, however, but the bladder was markedly irritated and the patient developed a suppurative epididymitis. Further work on many organic acids has been continued. The solubility effect and the irritability effect of various acids at different concentrations and pH levels have been studied. No acid better than citric acid as a solvent has been discovered, but it has been learned that the addition

# DIET FOR USE WITH AMPHOJEL REGIMEN

	Amt (cc. or gm)	Household Equivalents	Ca (gm)	P (gm)	Prot. (gm)	Fat (gm)	Car bohy drate (gm)
<i>Breakfast</i>							
Orange juice	100	1 cup	0.025	0.019	0.9	0.2	11.2
Oatmeal, or Grapenuts	20	2/3 cup 1/3 cup	0.016	0.073	2.8	2.8	13.6
Shredded wheat Bread, white		1 biscuit 1 slice					
Egg	50	1 egg	0.029	0.112	6.4	5.7	0.3
Bread white	60	2 slices	0.030	0.060	5.1	1.2	31.3
Butter or margarine	20	2 pats 2 pats	0.003	0.003	0.1	16.2	
Milk	90	2/3 cup	0.106	0.083	3.1	3.5	4.4
Sugar	65	3 tablespoons					64.6
Coffee or tea							
<i>Lunch</i>							
Grapefruit juice	200	3/4 glass	0.020	0.034	0.8	0.2	32.2
Carrots, or Cabbage	100	2 medium size 1 heaping cup	0.042	0.040	1.2	0.3	9.3
Onions		1 cup					
Parsnips		2/3 cup					
Spinach		1/2 cup					
Peas, or Brussels sprouts	100	1 level cup 1 cup	0.023	0.122	6.7	0.4	17.7
Cottage cheese		1 tablespoon					
Lettuce	20	2 small leaves	0.010	0.006	0.2		0.5
Tomato	100	1 medium size	0.011	0.027	1.0	0.3	4.0
Bread	60	2 slices	0.030	0.060	5.1	1.2	31.3
Butter	20	2 pats	0.003	0.003	0.1	16.2	
Milk	180	1 full cup	0.212	0.168	6.3	7.0	8.8
Apple or Cake	150	1 large serving 1 average serving	0.010	0.016	0.4	0.6	22.3
Fruit pie		1 average serving					
<i>Dinner</i>							
Meat or fish lean	100	1 medium serving	0.013	0.204	19.7	8.0	
Potato	150	1 large	0.019	0.079	3.0	0.1	28.6
String beans or Asparagus	100	1 cup 8-10 spears	0.065	0.044	2.4	0.2	7.7
Cauliflower		1 cup					
Squash		1 cup					
Turnips							
Lima beans, or Corn	50	2 tablespoons 1/2 cup	0.015	0.056	10.3	0.6	30.8
Brussels sprouts		1 tablespoon					
Bread white	60	2 slices	0.030	0.060	5.1	1.2	31.3
Butter	20	2 pats	0.003	0.003	0.1	16.2	
Cherries, or 1 car	100	2/3 cup 1 medium serving	0.017	0.022	1.1	0.5	17.8
Fruit pie		1 average serving					
Cake		1 average serving					
Coffee or tea							
Total Calories	2,540	Total Grams	0.730	1.310	82.0	82.0	377.0

of magnesium ions to certain organic acids, including citric acid, reduces their irritability.<sup>5</sup> Solution "G," the formula of which is given, has been used with good effect in many patients.<sup>6</sup>

*Solution "G"*

Citric Acid (monohydrate)	32.25 gm
Magnesium Oxide (anhydrous)	3.84 gm
Sodium Carbonate (anhydrous)	4.37 gm
Water	qs ad 1000 cc.

(This solution may be autoclaved)

The efficacy of retrograde dissolution of stones with Solution "G" is dependent first on the fact that the stones are composed of calcium phosphate (or calcium carbonate, or magnesium ammonium phosphate), secondly, it is dependent on the ability of the patient to toler-

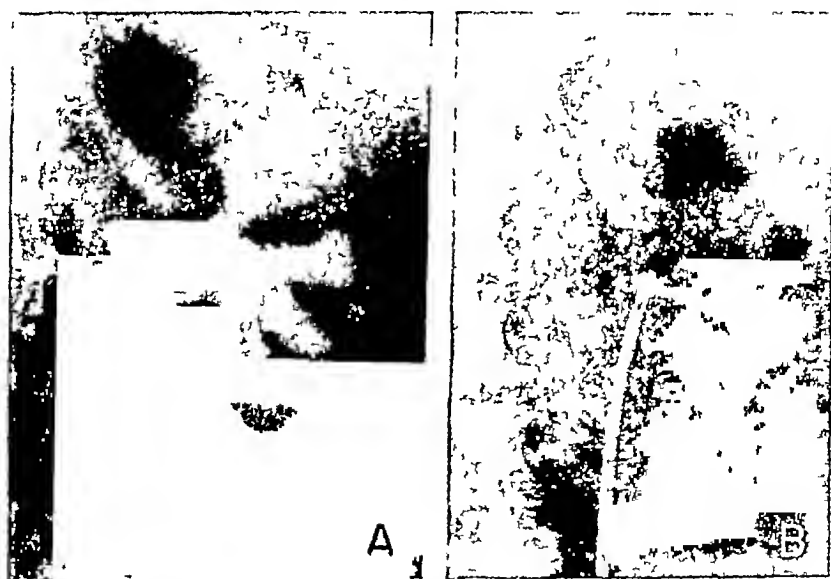


Fig 168—Roentgenograms of patient treated by retrograde dissolution with Solution G. A, Before dissolution. A large staghorn calculus fills the entire kidney pelvis and calyces. B, After forty days of dissolution treatment. The large staghorn calculus has been almost completely dissolved by retrograde irrigation through a ureteral catheter.

ate the solution. Most people, however, tolerate it well. Thirdly, it is dependent upon the ability to get and keep the solution in contact with the stone. This puts the problem up to the ingenuity and patience of the attending urologist. In certain patients who have stones that are embedded in a blocked calyx or in inspissated pus, it will be impossible to get any practical results by this method. In most patients, however, certain mechanical methods which will be effective can be improv-

vised. Sometimes it is practical to introduce the solution through a nephrostomy tube and allow it to drain down the ureter and into the bladder. A situation where this method is feasible often occurs in patients whose stones were incompletely removed at operation. If these patients cannot tolerate the solution running into their bladder, the solution can be introduced through a No. 10 Bardam ureteral catheter and allowed to irrigate the stone and drain out the nephrostomy tube. In a small group of patients whose ureteropelvic junctions are not open, a two-way nephrostomy tube can be utilized. The method of choice, of course, though often not feasible, is to dissolve the stone through a ureteral catheter, using either a two-way ureteral catheter or back and forth irrigations in a single barreled No. 10 Bardam catheter. Figure 168 shows a large staghorn stone which was dissolved through a ureteral catheter by solution. G

Retrograde dissolution of stones is still in its infancy. There are many difficulties which are encountered: pain in some patients, bouts of pyelonephritis, occasional bleeding, long duration of the program. These problems are the ones which the patient and the urologist must meet and weigh in deciding whether or not this form of therapy is the most preferable one.

### CONCLUSION

Since urinary calculi may be of different chemical compositions (or mixtures thereof), it is always of the greatest importance that any stones which are passed by patients or surgically removed from patients be carefully analyzed. The result of the analysis will be of great importance in aiding the physician to prescribe a regimen most suitable for the specific case.

In studying a case of urolithiasis, one should always take a thorough history, including a family history and a complete history of dietary habits. The question of previous bouts of urinary infection should always be considered. A careful urinalysis including careful examination of the urinary sediment and pH determination of each voided specimen for two or three days should be done. The urine should be cultured. Blood determination of nonprotein nitrogen, blood calcium, blood phosphorus, alkaline phosphatase, serum protein, and blood uric acid should be made. A high blood calcium above 10.5 mg per 100 cc, with a low blood phosphorus below 2.5 mg per 100 cc, will be suggestive of hyperparathyroidism. A high blood uric acid above 5 mg per 100 cc will be suggestive of high uric acid excretion. A twenty-four hour sample of urine should be examined for total calcium, and amounts of 200 mg or more should be considered suggestive of hypercalcemia.



(i.e., hyperparathyroidism) It must be remembered that it is possible to have a normal blood calcium and phosphorus and still to have increased calcium excretion and hyperparathyroidism. A first morning specimen of urine should be examined chemically as well as microscopically for the presence of cystine.

From the knowledge of (1) the stone analysis (if available) or (2) the circumstantial evidence, the patient should then be placed on a regimen which would

- 1 Eliminate foods containing the offending crystalloid from the diet
- 2 Produce a urinary pH most favorable for solution of the offending crystalloid
- 3 Sterilize the urine (if infection is present)
- 4 Provide an intake of from 4000 to 5000 cc of fluid daily

The efficacy of any regimen naturally depends on the rigidity of its enforcement. Patients with urolithiasis, therefore, should be followed like patients with diabetes until they are completely cognizant of all the principles and facts utilized in their specific regimen. Above all, they should be made well aware of the importance of constantly adhering to their prescribed regimen. Here, indeed, can be preventive medicine.

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## THE TREATMENT OF RICKETTSIAL DISEASES

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AND

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The rickettsial diseases of man include typhus fever Rocky Mountain spotted fever rickettsialpox tsutsugamushi disease (scrub typhus) and Q fever The etiologic agents are microorganisms called rickettsiae which are visible in ordinary microscopic preparations as small pleomorphic cocco-bacillary forms. They occupy a position intermediate between viruses and bacteria

The treatment of rickettsial diseases depends upon an understanding of the pathologic processes which underlie these diseases It is important to recall that although the rickettsiae differ from one another in their antigenic composition all are obligate intracellular parasites and can multiply only within living cells In man the various rickettsiae invade the endothelial cells of small arteries capillaries and veins This pathologic process results in endothelial proliferation formation of mural and occluding thrombi perivascular infiltration hemorrhage and tissue necrosis Almost every organ in the body may be involved but the distribution and severity of lesions depends to a certain extent upon the particular type of rickettsiae In epidemic typhus and Rocky Mountain spotted fever the organs most frequently the site of rickettsial invasion are the skin brain and spinal cord heart kidneys liver and spleen In tsutsugamushi disease and Q fever the lungs are frequently involved No exanthem is present in Q fever In the newly described disease rickettsialpox complete pathologic data are lacking but the exanthem present in this disease indicates that the skin is affected Generalized small blood vessel damage by an invasive intracellular parasite, therefore is the chief pathologic feature of this group of diseases.

The clinical features of the rickettsial diseases show considerable variation in symptoms and physical signs Epidemic typhus fever murine typhus fever Rocky Mountain spotted fever and tsutsugamushi disease are characterized by high fever and a generalized maculopapular eruption which may become petechial and which involves

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The seriousness of renal impairment in typhus fever was pointed out many years ago. Its presence during the course of the disease is of ominous prognostic significance. Signs of renal failure usually appear between the eighth to twelfth days of the disease in typhus fever. A fall in the systolic blood pressure in the space of a few hours is frequently the first sign to indicate that oliguria and azotemia are imminent. The importance of frequent measurements of the blood pressure, therefore, must be further emphasized, particularly at a time when the rash is appearing. In typhus fever the prognostic importance of nitrogen retention is such that helpful information is obtained by frequent determinations of the blood urea or nonprotein nitrogen. A rapidly increasing nitrogen retention carries a poor prognosis.

The treatment of azotemia in these diseases has as its objectives the maintenance of an adequate urine volume and blood pressure. Usually the oliguria which so often appears at the time of low blood pressure lasts from one to four days. After this time, the patient either succumbs or the blood pressure begins to rise, the urine volume increases and recovery takes place. If by the judicious use of intravenous plasma, human albumin or whole blood, one can maintain an adequate blood pressure (usually above 90 mm systolic) during this critical period, recovery may be anticipated in a few cases. However, it should be noted that continued suppression of urine with increasing nitrogen retention may occur in patients whose systolic blood pressure has not fallen below 100 mm of mercury. Oliguria and nitrogen retention develop most frequently in patients whose rash becomes increasingly hemorrhagic, in whom the fever remains very high and in whom other overwhelming signs of rickettsial infection are manifest. The use of intravenous saline solutions in patients with oliguria is hazardous, although the hypotension which accompanies this condition in so many instances may be temporarily overcome by saline infusions, too often edema develops which is a serious complicating condition and is associated with a high mortality. In this regard it should be recalled that in typhus fever a reduction in serum albumin frequently is found during the acute phase of the disease.

**Bacterial Infections**—Secondary bacterial infections which develop during the course of a rickettsial disease may be serious and require prompt treatment. The use of penicillin or streptomycin is advocated, depending upon the susceptibility of the organisms encountered. The use of sulfonamides appears to have an adverse effect in rickettsial infections, consequently it is preferable not to use sulfonamides during the acute stage of a rickettsial disease. (Literature pertaining to general supportive measures reviewed by Yeomans,<sup>1, 2</sup> see also Ravenel<sup>3</sup> and Howell et al.<sup>4</sup>)



Mountain spotted fever (Rose, Duane and Fischel,<sup>22</sup> Flinn et al,<sup>23</sup> Ravenel<sup>24</sup>)

A summary of the results in the treatment of twenty patients suffering from louse-borne typhus (Snyder et al<sup>20</sup>) indicates that statistically significant differences were observed between PABA treated and control groups as regards duration of fever (see Fig 169), inci

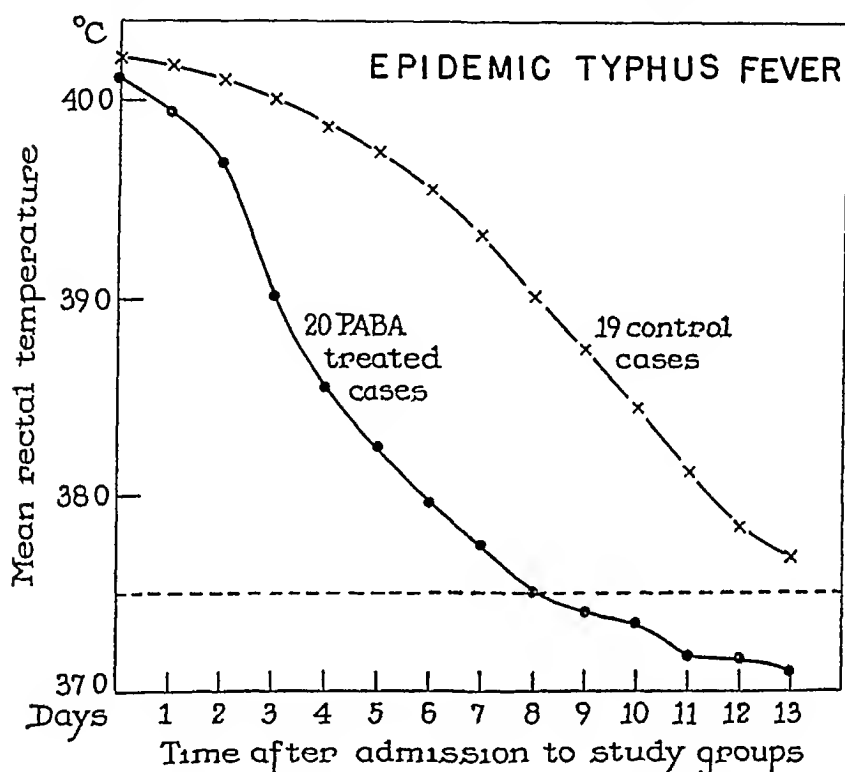


Fig 169—Effect of para aminobenzoic acid (PABA) on epidemic typhus fever. Comparison of temperatures of twenty PABA treated patients and nineteen untreated control patients Cairo Egypt 1911 and 1915. Mean daily rectal temperatures are plotted for each group, zero day being the day of admission of each patient to the study (the mean duration of illness at the time of admission for both groups was 1.4 days). The temperature of fatal cases are included up to the last reading before death occurred.

dence of complicating conditions, and case fatality rate. A significant correlation was observed among the PABA-treated patients between the duration of illness when treatment was begun and the final clinical severity as indicated by duration of fever plus incidence of complications. In the untreated group there was no such correlation. Best results were obtained with *early* treatment, that is, in the first ninety-six hours of clinical disease. The observations suggest that treatment

begun later than the eighth day of illness will not disclose differences between treated and control patients. A significant reduction in the percentage of polymorphonuclear leukocytes was observed in the PABA treated patients but no difficulties were encountered from agranulocytosis. Patients tolerated the drug well even those who were in very poor physical condition as a consequence of malnutrition or complicating diseases.

*Dosage of PABA*—It is important to administer a sufficient quantity of PABA to attain promptly and to maintain thereafter for the entire period of therapy a blood concentration of PABA (as free diffusible substance measured against a standard of PABA) of 10 to 20 mg per 100 cc. for patients suffering from typhus fever and from 35 to 50 mg per 100 cc. for patients suffering from tsutsugamushi disease and Rocky Mountain spotted fever. The drug as the free acid or the sodium salt when chemically pure is well tolerated by mouth. Since PABA is very rapidly absorbed and excreted it is necessary to administer it at frequent intervals throughout the day and night. The most satisfactory schedule for oral administration is as follows. The initial dose is roughly 0.05 gm per pound of body weight. This is followed by a dose of 1 to 3 gm every two hours day and night throughout the course of treatment. The blood concentrations are measured at frequent intervals to permit adjustment of dosage to attain an effective concentration. For determination of blood concentrations samples are obtained two hours following the last dose. At this time the measurement represents the lowest concentration in the interval between doses. It is particularly important to measure the blood concentration frequently in patients who have renal insufficiency or oliguria. Sufficient sodium bicarbonate is employed to maintain the reaction of the urine neutral or slightly alkaline. The occurrence of crystals of PABA in the urine has not been encountered but is a possibility that should be considered.

*Route of Administration*—Parenteral administration of PABA has been attempted in a few cases. It is the opinion of various authors that the use of intravenous pyrogen free buffered solutions of chemically pure sodium PABA probably would be a valuable adjunct to oral therapy for certain cases.

*Duration of PAB 1 Therapy*—PABA should be continued for forty eight hours after the patient's temperature has returned to normal. When PABA is withdrawn prematurely a mild febrile period probably representing a recrudescence of the disease may be observed in some patients.

*White Blood Cell Count*—The white blood cell count should be as

certained in every patient daily from the start of PABA therapy until the third or fourth day after treatment has been discontinued. If the white blood cell count falls below 3000 per cubic millimeter or if the polymorphonuclear leukocytes drop to less than 25 per cent, it must be decided whether these phenomena are of more serious prognostic import than the withdrawal of the inhibiting effect of PABA on the rickettsiae.

*Contraindications to PABA Therapy*—Contraindications to the use of PABA are the development of a white count below 3000 per cubic millimeter or a reduction of polymorphonuclear leukocytes to less than 25 per cent. The administration of PABA should be interrupted at once if crystals appear in the urine. PABA should be given by stomach tube to patients who are too prostrated by their disease to swallow properly; severe tracheobronchitis may result from aspiration of PABA. Renal insufficiency which may be present from the beginning of PABA therapy or which may make its appearance during the course of therapy is not necessarily a contraindication to continued PABA therapy; blood concentrations under these circumstances must be determined frequently in order that adjustments in dosage may be made to avoid excessive blood levels.

*Mode of Action of PABA*—The action of PABA appears to be rickettsiostatic. Its administration in adequate amounts does not result in an immediate drop of temperature to normal nor in the immediate disappearance of signs and symptoms of rickettsial disease. Instead the usual evolution of the disease appears to be arrested at whatever stage the illness had attained at the onset of therapy. Then in the course of three or four days, perhaps longer, the natural defenses of the host slowly overcome the infection. The development of antibodies and the establishment of immunity appear to be in no way altered by the use of PABA. Contact in vitro between PABA and various rickettsiae does not affect their viability or their toxic properties.

*Fate of PABA in the Body*—Some PABA is conjugated with glycine to form para-aminohippuric acid which is entirely inert against various rickettsias in experimental infections. A small amount of PABA is acetylated. Acetyl PABA, para-aminohippuric acid, and PABA itself are very rapidly excreted in the urine.

#### SUMMARY

Specific immune serum appears to be effective only if administered very early in the course of classical typhus and Rocky Mountain spotted fever. Penicillin, although effective in laboratory tests with murine typhus, has been disappointing in clinical trials. Streptomycin has a

slight activity against typhus but not tsutsugamushi infections it has not been tested clinically. Two new antibiotics chloromycetin and A377 offer considerable promise but clinical trials have not been reported.

The strongly antirickettsial substances para sulfonamidohenzamidine and methylene blue appear to be limited in value by their toxicity for man. A nitroacridine derivative merits further clinical trial. An antimalarial compound *sontoquin* was stated to affect favorably the course of classical typhus in French North Africa.

Para aminobenzoic acid has had the most extensive clinical trials of the recently discovered chemotherapeutic agents having been tested against classical typhus murine typhus Rocky Mountain spotted fever and tsutsugamushi disease in man. It has not been used in Q fever or trench fever. To date experience indicates it is safe for human use. If begun early and given in large amounts it appears to be effective in arresting the progress of several rickettsial diseases of man.

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## THE TREATMENT OF MIGRAINE

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It is common parlance to speak of any trying exasperating problem as a "headache." This expression may be applied very aptly to the problem of treating headache itself. Certainly the multitude of theories concerning the proper handling of patients with headache and the demands which these patients place upon the busy practitioner's time are enough to discourage him at the outset when this problem is presented to him. It is a natural reaction for the doctor in the press of time to prescribe for the headache victim a pain killing medicine in the hope that such a measure will allay the present attack and that the next one may be dealt with on the same superficial plane when it occurs.

Such an approach is no doubt successful in dealing with a large percentage of mild nonspecific headaches but it is not satisfying to the patient who is suffering from repeated attacks of severe migraine. Any doctor who has seen his patient in a full blown migraine attack will realize that it is a violent experience the frequent repetition of which may make serious inroads on life and livelihood and in some cases actually cause total incapacity. The migraine symptom-complex is one which follows its victim for years, has its roots firmly embedded in the heredity and total background of the patient and requires a thorough resourceful and sympathetic medical handling as other major disorders such as peptic ulcer. To leave the migraine patient with the sole recommendation that he take a certain pain killer when he has his attacks is equivalent to leaving the ulcer patient with the sole advice that he take sodium bicarbonate when his stomach hurts. Superficially and temporarily such measures may be effective in both instances but the fundamental process is not altered. The first step therefore in the treatment of migraine is the development in the doctor of an appreciation of the magnitude and depth of the problem and a willingness to meet with patience and his best efforts the challenge which is presented.

The second step in the treatment is the development of a corresponding attitude in the patient. The migraine sufferer is very apt to shop around among doctors in search of a quick cure. It is important that he be made to understand from the outset that the treatment of his ailment requires considerable time, several visits, and close attention to rules and regulations on his part. Instances are few indeed in which

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the migraine sufferer is cured of his disease in the sense that he never has another attack. If, however, patient and doctor are willing to work together over an extended period, much may be offered to the patient in changing an unbearable situation to a tolerable one, compatible with a reasonably happy and successful life.

#### DEFINITION

Before going further, it is important to define what is meant by migraine in this discussion. There are almost as many definitions of migraine as there are authors who write about it, largely because the malady is so protean in its manifestations. This variability of symptomatology takes place not only from patient to patient but also within the history of a single patient. Thus one patient may always have attacks starting with scotomas and followed by headache, lasting only a few hours, and another patient may have attacks of unilateral pain associated with violent nausea and lasting several days. A third patient may have both of these types of attack at different periods of his life, and a fourth may have only periodically recurring bilateral headaches. Are these all migraine, or is each a separate entity? It is my opinion that when these variants have the added features of periodicity, a strong family history, and a lack of organic etiology, they may be listed under the general heading of migraine. It is well to remember that periodic headaches may gradually come to occur more and more frequently until the patient is experiencing almost constant headache. The fact that it is constant may lead one to think that the headache is on some other basis, but a careful history of the development of the difficulty through the years may supply a strong suggestion that the constant headache is really a persistent attack, or a perpetually recurring series of attacks, of migraine.

Several schools of thought have developed which have attempted to explain migraine on an allergic basis, on an endocrine basis, by dietary imbalance, or by various anatomical, physiological, or psychological abnormalities. Each of these theories probably represents a part of the truth, but only a part. A broader concept suggests that the migraine victim has inherited from his forbears a pattern of reaction with which he responds to any one or all of these factors. If this concept is correct, the migraine sufferer is a person who has inherited a sensitive mechanism which reacts with explosive violence to a number of stimuli in his total bodily economy and environment.

From a therapeutic standpoint we are able to do little to change the patient's inheritance. We can, however, attempt with considerable success to adjust his environment and way of life in such a way that the

constellation of factors which is necessary to produce an attack occurs less frequently. If the doctor can on the one hand reduce or remove sources of irritation in the patient's environment and on the other increase the patient's emotional or physical capacity to meet his environmental strains, the number of migraine explosions will be materially reduced.

#### HISTORY, PHYSICAL EXAMINATION AND LABORATORY STUDIES

The most important step in the approach to the problem is to obtain a history which will bring to light as many facts as possible bearing on the nature of the attacks and the total medical history and life situation of the patient. Therefore it seems worth while to list certain headings which may prove useful as a guide to collecting pertinent data from a migraine patient. Under these headings I propose to make a note which explains in more detail the facts which are to be sought and their possible usefulness.

After the usual recording of age, marital status, occupation, address and telephone number, one settles into the actual headache history.

##### Previous Headache History

The age at which headaches of any type first appeared, the nature of these early attacks, their frequency and severity, and circumstances relative to their occurrence.

##### Present Headache

A detailed account of exactly what happens in the attack from the time of its first warning until it is completed, specific information about the location and type of pain and accompanying phenomena.

##### Duration

The length of the shortest, longest and average attacks.

##### Frequency

A statement regarding how many headaches occur per day or per week or per month.

##### Associated Phenomena

A check list for catching interesting details related to the attack: warning, scotomata, paresthesia, nausea, vomiting, sore neck, fluid balance changes, oculomotor disturbances, paralysis, aphasia, vertigo, pupillary changes, lacrimation, unilateral sweating, blocked nose, sudden or gradual onset and cessation, unconsciousness.

##### Mode of Relief

An account of what the patient does himself to hasten his attacks.

##### Effect of Cynegon

An inquiry as to whether cynegon has been used for what it was intended for, and with what results.

##### Previous Prophylactic Therapy

An account of what measures the patient has employed to prevent attacks.

prevent the occurrence of attacks, such as hormones, histamine, vitamins, osteopathy, sinus treatments, correction of refraction difficulties, diets

#### Patient's Correlation

The patient is given an opportunity to express, without any leading suggestions from the doctor, factors which he thinks precipitate attacks

#### Doctor's Correlation

The doctor inquires in detail about the relationship which the following may have to the onset of attacks: use of eyes, nose and sinus difficulties, dietary factors, allergic disturbances, chocolate, fatigue, emotion, menses (with a detailed account of the menstrual history and any gynecological operations), time of day, day of the week, tobacco, alcohol, season, place

#### Head Injury

An account of any head injury and its relation to the onset of the headaches

#### Pregnancy

The effect of pregnancy on the occurrence of attacks

#### Family History of Headache

A detailed inquiry into what members of the family have had 'sick headaches,' including aunts and uncles and grandparents as well as the immediate family

#### Family History of Epilepsy, Hypertension, Nervous Disorders

#### Past Medical History

An inquiry of the type which is obtained for any medical condition into any illnesses of importance which the patient may have had

#### Patient's Day and Diet

This is the most important part of the history. The doctor should follow the patient through every hour of the day from the time he arises, examining in detail his activities, in and out of the home, with notes on what is eaten at each meal, when the meals are eaten and how long it takes to eat them. This account should carry through the patient's entire day, and include notes on how much exercise, relaxation and sleep is obtained, the hour of going to sleep, and the hour of waking. By the time this part of the history has been completed, the doctor should have obtained an idea as to what kind of house the patient lives in, who else lives there, and the ways and habits, not only of the patient, but of the whole household. He should make a special inquiry as to what happens on holidays and week ends, and how much and what type of vacation is enjoyed by the patient.

#### Life Situation and Problems

The foregoing account of the patient's day serves as a suitable introduction to the personal and environmental factors that may be a source of stress in the patient's life. Under this heading should be outlined the problems which exist between the patient and his spouse, parents, in-laws, children, employer, church and economic situation.

A complete physical and neurologic examination is then in order, with especial attention to the condition of the eyes, nose, sinuses, teeth, cranial arteries, neck posture, blood pressure and thyroid status.

Laboratory examination should include as routine a Wassermann or equivalent test a complete blood count and a urine examination. Other special tests such as blood chemistry x rays lumbar puncture electroencephalographic and endocrine studies may be done as indicated.

A very important part of the history and physical examination is obtained by witnessing the patient during an attack at his home. This means that the doctor should tell the patient at the first interview that he would like to be called to the home in case an attack occurs. By this means he is brought face to face with the environmental factors and personnel who may play a large role in his patient's disorder. Thereby he may also be able to witness and judge better the severity of the attack and carry out certain special tests which may ultimately prove of importance in guiding treatment. Not infrequently it is by such visits that one discovers difficult personalities and difficult home situations which the patient has failed to reveal in the official history. It is also by such visits that one learns details of the attack such as the exact location of the pain the extent of physical or neurologic abnormalities the effect of various test drugs and in some instances the effect of injecting novocain around nerves or arteries which may be incriminated in the attack.

The doctor should bear in mind while he is taking this history and doing this physical examination that he is attempting to find factors in the patient's way of life which may serve to upset the delicate mechanism responsible for migraine attacks. Some of the errors in living which seem to be common to migraine patients are listed below.

1. Getting up too late in the morning so that the period between rising and the morning deadline of getting to the office or getting the children off to school is rushed and confused and sets an atmosphere of tension for the day.

2. Sleeping too late on Sundays and holidays. These days are favorites for the occurrence of migraine attacks, and the latter may sometimes be avoided by having the patient get up at his usual hour and take a rest later on in the day.

3. Eating a very scanty breakfast and a quick pick up lunch and settling down at the end of a tiring day to devour an unusually large dinner. A more even distribution of food energy during the day often proves beneficial.

4. Working steadily through the day without any breaks. A fifteen minute period of relaxation in midmorning and midafternoon is advised.

5. Staying up too late at night.

- 6 Insufficient time off and failure to take vacations
- 7 A tendency to pack too many events into any one day or week
- 8 An undue conscientiousness about neatness of the household or accuracy of work, coupled with an unwillingness to delegate tasks to others
- 9 Families living at too close quarters with in-laws
- 10 A tendency to take on extra activities, such as extension courses and public or church functions, when the schedule is already overloaded
- 11 A tendency to eat an excessive amount of carbohydrate food
- 12 Consumption of chocolate Chocolate is a common enough factor in producing headache so that it should be routinely eliminated in all forms from the migraine patient's diet

### PROPHYLACTIC TREATMENT

The migraine patient comes to the doctor in search of help on two scores first, how to prevent attacks and, second, how to mitigate such attacks as may occur

In regard to prevention of attacks, the doctor should review the information which has been gleaned from the history, physical examination and laboratory data, as obtained above, and see what he can do to correct any deficiencies which have become apparent This measure may include such things as correcting anemia, administering thyroid for low metabolism, reducing menopausal symptoms by the judicious use of estrogens, as well as effecting the alterations in the patient's way of life and diet and personal relationships which are suggested by the topics outlined above Since measures of this type are probably of the most fundamental importance over the course of the years, it is well to give the patient a two or three months' trial on these alone before resorting to other medical "tricks" which at times may prove useful, but which really should serve only as adjuvants to the basic regime Some of these medical "tricks" are the use of histamine desensitization, nicotinic acid sedation, antihistamine drugs and elimination diets Any one or all of these measures may prove helpful in getting the migraine victim around a particularly difficult corner, or in helping the patient who finds it impossible for one reason or another to follow the fundamental rules In the long run, however, it is not wise to let the patient pin the success of the treatment on any one of these measures to such an extent that he forgets the fundamental importance of a temperate way of living It is well known that migraine usually responds temporarily to any new treatment, but, in most cases, long lasting relief comes not out of a bottle or syringe, but out of a way of life

The following case histories are submitted as examples of these principles

CASE I—A single, 54 year old music teacher and church organist complained of having severe attacks of left sided headache involving the region of the left eye, left temple and left occiput ever since puberty with an increase of frequency and severity of the attacks during the past eight years until they were occurring once every two weeks and causing her to lose one or two days of work on each occasion. They were accompanied by nausea and vomiting and severe prostration. Her mother had had similar severe sick headaches. The attacks had increased in frequency since the cessation of her menses one year before.

The patient's working day was filled with a variety of tasks, including music lessons, funeral services, choir rehearsals, Sunday church services and organ recitals. Her duties required that she hurry from one part of town to another to meet fixed appointments in such a way that she often missed meals or ate them hurriedly at irregular hours. She had recently undertaken the job of improving the choir and church music at a large church where many forceful personalities had to be dealt with effectively. Her headaches were very apt to occur on Saturday morning after Friday night's intensive choir rehearsal. She was an ambitious person and one who strove mightily to produce the very best in music and to fulfil with perfection the requirements of her jobs. Rheumatic heart disease as a child had left her with mitral and aortic regurgitation. She and her sister lived together and depended upon their own efforts entirely for their livelihood. She had not taken a real vacation for several years.

This patient was frightened by the increasing incapacity caused by her headaches and was most assiduous in carrying out directions. These consisted in instructing her (1) to get up on time each morning, (2) to have her meals on time, (3) to take time for her meals, (4) to discontinue her practice of giving a music lesson after dinner at night, (5) to take Friday afternoon off for rest before choir rehearsal, (6) to have a rest of fifteen minutes in the morning and half an hour in the afternoon daily and (7) to plan in advance a vacation for the following summer.

The patient was already taking moderate doses of estrogenic substance for mild menopausal symptoms. This was continued. She was also taking vitamin B<sub>12</sub> by injection every other day and since she placed great faith in this measure this was continued. On this regime her headaches soon lessened in severity and frequency and after a month ceased entirely for a period of over a year. Recently there has been a mild recurrence of headache during a period in which the type of music which she was producing in the church was criticized by an influential person in the choir.

CASE II—A 21 year old single girl, a college student, complained of headaches characterized by severe scintillata lasting as long as an hour followed by moderately severe headaches lasting one to three hours. She had suffered no headaches until she entered college. In her first year



she had had only occasional attacks, but during her sophomore year she had had two periods in which attacks came every day for a week or more. In her junior year there had been two periods in which attacks came every day for a week, and one in which they occurred once, and occasionally twice a day, for three weeks. This last siege was severe enough to cause serious inroads upon her studies. In her senior year she had been having attacks every day for over a month. Her father and mother both have periodic headaches. Her physical and neurologic examination revealed no abnormality.

In going over her daily program, it was found that she tended to get up late in the morning, eat no breakfast and only a very sketchy sort of lunch, and have a rather large meal in the evening, containing a high starch and low protein content. She rarely went to bed until one o'clock in the morning. During the school year, when she was living away from home, she tended to eat much more candy, especially chocolate, than when she was at home. She also drank cocoa two to three times a week, and had chocolate ice cream twice a week.

She was asked to get up earlier in the morning, to eat a good breakfast, to form a good bowel habit, to get half an hour of mild exercise, out of doors, four times a week, to get to bed on three nights a week by eleven o'clock, and to omit chocolate in any form from her diet. In addition, she was asked to take pyribenzamine, 50 mg, four times a day. On this regime, and with this medication, her headaches promptly stopped and have not recurred during the past three months.

**CASE III**—A 50 year old married minister suffered severe periodic attacks of headache associated with nausea and vomiting, and some blurring of vision. His father had had very severe "sick headaches." Gynergen would relieve his attacks, but made him feel sick and caused his extremities to be numb. Dihydroergotamine was slower in stopping the headaches, but was of great help and had no untoward side reactions. Although this man's headaches had started at about the age of 20 when he had one or two attacks per year it was not until he went to take his first post as a minister in an important church that his headaches became a real problem. He was a very energetic man, very ambitious and a good preacher. With increase of work and church responsibilities, his headaches became so frequent and severe that he sought relief from various large clinics and leading specialists. He underwent many x-ray and laboratory investigations, including pneumoencephalography and electroencephalography. He had mild hypertension. Finally he was told, after seven years of suffering, that he must give up his church work and retire. Although his inherent ambition strongly rebelled against such a move, his doctors frightened him sufficiently with threats of "strokes" so that he gave in to their wishes, and, leaving the full, active, energetic life which he so relished he retired to a small island in Maine. His headaches, to be sure improved somewhat on this regimen, but he was most dissatisfied with his inactivity, and finally took it upon himself to start a radio preaching program which soon assumed large proportions and took

him to New York City. While engaged in this project of his own making although he was working with great intensity his headaches ceased entirely for a period of several months. The program came to an end however and he had to return to a life of inactivity, worries about his livelihood and problems of illness among other members of his family. With this change his headaches recurred and regained their original intensity and frequency. His doctors made a final pronouncement and ordered him never to work again but to retire to his island for the rest of his life. This prospect made him very miserable indeed and his headaches went on with unabated fury.

When this problem was reviewed a program was outlined for him whereby he undertook the pastorate of a university chapel in which the conflicting demands of various cliques in the parish were absent and there was ample opportunity for this man of real ability to gratify his desire to do good work with youth without too much expenditure of mental and physical energy. Although his headaches continued to occur they were distinctly less frequent and severe and his whole outlook on life was changed from one of looking forward to hopeless invalidism to the encouraging prospect of carrying on useful work in the future.

#### TREATMENT OF THE ATTACK

The treatment of the actual attack of migraine varies according to the intensity and duration of pain. If the attacks are mild and of short duration they may be controlled adequately by the use of aspirin. If they come at rare intervals and cannot be controlled by aspirin alone it may be safe to use codeine in addition but resort should not be made to this drug if the attacks are frequent for fear of producing addiction. Usually the pain of migraine is so severe however that these drugs are not very effective in stopping it.

Ergotamine tartrate is the most effective weapon against the migraine attack. It stops the headache in 80 to 90 per cent of cases when given hypodermically and in about 30 per cent of cases when given by mouth. It is probably wisest to test the effectiveness of this drug therefore by giving it hypodermically in doses of 0.5 mg subcutaneously or intramuscularly. Once the patient has gained confidence that he has found a medicine which will stop his attacks, he will be willing to experiment with dosage and route of administration. But if he receives it first by mouth and it fails, he may lose faith both in the medicine and in his doctor.

Arrangements may be made with the local district nurse for this test injection. If it proves effective the patient or a member of his family should be instructed in the hypodermic technique.

Not infrequently 0.5 mg of ergotamine tartrate injected parenterally causes unpleasant side effects such as nausea and vomiting.

cramps and general lassitude. It is a common experience to find, however, that reduction of the dose to three quarters or one-half this amount may still meet with success in stopping a headache without producing toxic symptoms. Should these symptoms persist in the face of the reduced dosage, two courses are open: (1) to combine with the injection of ergotamine an injection of 0.6 mg. of atropine sulfate and 0.25 gm. of caffeine sodium benzoate, or, (2) to use the more recently developed dihydroergotamine (DHE45) in a dose of 1 to 2 mg., injected intramuscularly or subcutaneously. This new derivative of the ergot group of alkaloids may often be tolerated when ergotamine tartrate itself is not.

When ergotamine tartrate is given by mouth, the dosage may range anywhere from 1 to 10 mg. during an attack. Most patients require about 3 mg. as an initial dose. This may be followed, at hourly intervals, by 2 mg., until the headache has ceased, toxic symptoms have developed, or a total of 10 mg. has been reached. Recently it has been found that a combination of ergotamine and caffeine is a good one. Pills and rectal suppositories containing this combination may soon be on the market. At present, the addition of 100 to 200 mg. of caffeine to the first dose of ergotamine given by mouth, and its repetition if necessary after three or four hours, will prove of real benefit in some cases.

Ergotamine tartrate, because of its vasoconstrictor action, is contraindicated in hypertension, marked arteriosclerosis, coronary disease, peripheral vascular disorders and hepatic dysfunction. Neither should it be used in pregnancy, because of its effect upon the uterus. Dihydroergotamine is a less powerful vasoconstrictor, but should, nevertheless, be used only with great caution in the presence of vascular disease, since, in order to obtain results in stopping headache, some vasoconstriction is required. The effect of dihydroergotamine on the uterus is alleged to be minimal, but the author cannot speak from his own experience on this point.

The question frequently arises as to how often these drugs may be used. If the contraindications noted above are observed and the patient manifests no untoward reaction to the first few doses, these drugs may be used as frequently as two or three times a week. In using any of them, it is well to remember that they are much more effective when given as soon as possible during the attack. The patient should be instructed to administer them as soon as he is sure that he is having a genuine attack of migraine.

There are some patients whose attacks do not respond to the ergot derivatives or to codeine and aspirin, and for whom the doctor is forced

at times to resort to the use of demerol or morphine. Such drugs should never be given to the patient for self administration but should be kept within the doctor's power to give or deny since the danger of addiction in this chronically recurring ailment is great. Other measures for treating the migraine attack have been recommended such as the use of nicotinic acid by mouth or intravenously in doses of 50 to 100 mg., and the inhalation of 100 per cent oxygen for a period of an hour. Intravenous administration of 30 mg. of benadryl hydrochloride has proved effective in the author's hands in one instance, when other measures had failed. These drugs are worth remembering in occasional cases but the inconvenience associated with their administration detracts from their value as routine therapy. The use of sedatives such as phenobarbital or pentobarbital in addition to any of the above forms of treatment may prove beneficial in some instances in which restlessness and nervousness are prominent symptoms. Such sedatives should be prescribed only in small quantities at a time, however, because of their habit forming potentialities.

### SURGICAL TREATMENT

Surgery for the relief of migraine should be reserved for those patients who are still having severe and frequent attacks of pain in spite of having given conservative medical measures a prolonged and thorough trial. Even then the doctor should proceed with caution in the selection of patients and procedures. Surgery for the relief of pain about the face and head has a well recognized tendency to make matters worse if it does not make them better. If there are strong emotional factors at work in producing the patient's pain or strong psychoneurotic traits in the patient's personality surgery should be suggested only after expert psychiatric opinion has been obtained. It is wise, whenever possible to mimic the effects of surgery with novocain block before proceeding with definitive measures. Surgery should be considered only for patients whose pattern of headache is relatively the same from attack to attack and is limited to a definite area. In all cases one should be sure that the symptom is not caused by organic disease which might be masked by surgery.

The measures which have been employed for this purpose have been (1) section of sensory nerves (2) operations on the sympathetic nervous system and (3) ligation and section of cranial blood vessels and the nerves in their sheaths.

Of these procedures the last is the least damaging and in some instances has proved of considerable benefit. Ligation and section of one or several branches of the external carotid artery or of this artery

itself have in some cases been worth while. In others, the relief has been incomplete or temporary or both.

These principles are illustrated in the following case histories.

CASE IV—A 22 year old college student, male, had suffered for a year and a half with recurrent attacks of severe headache in the left temporal region, radiating into the left orbit. These recurred periodically and finally had built up to a frequency of approximately three times a week. Pressure on the left temporal artery and novocainization of the left temporal artery as it passes anterior to the ear consistently brought relief of the headache on three separate occasions. The artery with its perivascular tissues was ligated and a section removed. When last heard from the patient had had no subsequent attacks for two years. The pathological report on the tissue removed revealed no evidence of temporal arteritis. The diagnosis of migraine in this case is not completely clear, but it is offered as an example of periodically recurring localized headache relieved by a simple surgical procedure, after preliminary testing with novocain.

CASE V—A woman 40 years old had suffered from severe attacks of unilateral headache associated with nausea and vomiting and ringing in the ears for several years. Conservative measures had failed to bring any but temporary relief. Manual compression of the temporal artery during a headache gave partial relief and similar compression of the common carotid gave complete relief while the pressure was exerted. The attacks of headache had become gradually more and more frequent until finally there was continuous headache and total incapacity. A complete neurologic examination failed to reveal evidence of organic disease. The external carotid artery on the left side was ligated and cut. The severe pain was relieved and the patient was able to resume her activities, although occasional attacks of migraine, involving the right side, continued to occur. This relief has lasted seven years but there are now indications that a return of the former pain may take place since the patient is beginning to experience pain again behind her left eye and in the left occiput.

CASE VI—A 34 year old woman complained of very severe left-sided headache, associated with nausea and vomiting for ten days out of each month at the time of her menstrual period. Medical measures brought no relief, and the patient's general health was being seriously impaired. Compression of the left common carotid gave temporary relief to pain during attacks. The left external carotid artery was ligated and cut and for three months the pain of the attacks was completely absent although the vomiting and prostration took place as usual. After this the pain recurred and continued unabated.

Sympathetic surgery, such as operations on the stellate and superior cervical sympathetic ganglion, although not personally tried by me,

would seem from the literature to offer little of lasting value. Alcohol injection of the ganglion of the fifth nerve and surgical section of its posterior root have proved to be effective in isolated instances but inasmuch as they are major procedures and cause a permanent sensory defect they should certainly be used only in extreme cases. The same may be said for section of the sensory root of the fifth nerve in the medulla which has been reported as effective in stopping the pain of certain periodic headaches.

In general the resort to surgery as a means of treating migraine is to be discouraged unless all other measures have failed and the patient is greatly incapacitated by his symptoms. When used at all it should be carried out by an accomplished neurosurgeon after thorough medical, psychiatric and neurologic consideration.

CASE VII—A 34 year old married housewife, with a strong family history of sick headaches in her mother and two sisters had had severe left-sided headaches, associated with nausea and vomiting of marked degree since puberty. They had finally become so incapacitating nine years ago that neurosurgery was contemplated for relief. The posterior root of the left fifth nerve was injected with alcohol with resulting hemianesthesia of the entire face and forehead. No headaches on the left side have occurred since this procedure for nine years. Two years ago however the patient began to have attacks of a similar nature on the right side once a month at the time of her periods. These could be relieved by the injection of 0.5 mg. of ergotamine tartrate. This medicine however caused severe prostration and left her weak and nauseated for the rest of the day. The substitution of 1 mg. of dihydroergotamine proved to offer a successful means of stopping her headaches without the prostrating effect of gynergen.

In conclusion the author wishes to stress again the fact that the success of treating the migraine patient depends largely upon the thoroughness, perseverance and resourcefulness which the doctor is willing to apply to a detailed and prolonged therapeutic relationship with his patient.



# THE MODERN TREATMENT OF RHEUMATOID ARTHRITIS

THEODORE BEVIER BAYLES M.D.\*

There is no specific treatment for rheumatoid arthritis, as there are no known proven etiologic factors in this disease. However through the years, certain procedures have been found to be of unquestioned value and many more discarded because of their failure to alter the course of the disease satisfactorily. In this clinic I shall outline the former.

Rheumatoid arthritis varies in the individual patient from mild arthralgia and intermittent periods of mild joint swelling over a period of many years to an acute widespread inflammatory disease involving the connective tissue of joints, nerves, muscles, heart, tendons and other organs. In this latter group there may be high fever, pleurisy, pericarditis, anemia, polymorphonuclear leukocytosis, marked weight loss and permanent crippling of the joints in a few months. Obviously the course of the disease alters the intensity of the treatment which is carried out. However the mild case may suddenly become fulminating in character and since, even in the mild form, the disease may produce permanent crippling of the patient insidiously over a period of years, it is the opinion of this author that every patient with this disease should be given every chance to get rid of this abnormal process or reaction in the body.

As in rheumatic fever, glomerulonephritis, erythema nodosum, lupus erythematosus, disseminatus, periarteritis nodosa and the other members of the collagen disorder group, the reason for the development of rheumatoid arthritis in a patient living in the same environment as his fellow man, with the same emotional problems, the same passing or chronic infections, the same endocrine waxing and waning and the normal American diet, has not been established. The problem can best be appreciated if we look upon this unfortunate individual as decompensated or deficient or even different than his fellows. Certainly the high incidence of rheumatoid arthritis in families and of rheumatoid spondylitis in twins supports the concept that the inheritance of the individual is important. The most fashionable and acceptable theory for the etiology of rheumatoid arthritis places this disorder in the group of diseases thought to be due to tissue hypersensitivity. There

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is considerable evidence in experimental work in relation to *apparently related* disorders which substantiates this concept. But, as Baehr and Pollack<sup>1</sup> have pointed out, the finding of fibrinoid degeneration of collagen and inflammatory changes in connective tissue is not sufficient to prove adequately such a theory, as the tissue reactions might result from any toxic reaction or abnormal metabolite, and not necessarily from an antigen-antibody reaction. The same warning might be made in our thinking concerning rheumatoid arthritis.

In any event, the connective tissue reaction, especially in areas of tissue motion such as the joints or in areas of tissue trauma such as the development of nodules over bony prominences, is helpful in establishing fundamental concepts of preventing more inflammation and permanent change to these structures. This local treatment of tissues, plus the concept of the "decompensated" individual, are the cornerstones of successful therapy in rheumatoid arthritis.

In the minds of some physicians rheumatoid arthritis is a mild bothersome condition which is best handled by neglect or some cursory directions such as "take some aspirin, get lots of rest and sunshine and eat lots of good food and, above all, don't worry." This in my opinion is a dangerous attitude for the patient, his or her family and the physician responsible for the care of the patient. As a starting point in therapy I should like to present the early life history of a fulminating case of rheumatoid arthritis.

### CASE REPORT

J. S. (Case No. 3274), a 55 year old white man, a Swedish American stone cutter, was admitted to the Robert Breck Brigham Hospital on November 25, 1947. The patient was perfectly well and working steadily until September 11, 1947, when he alleges he strained his left arm and shoulder and that night had severe pain in this arm and shoulder. On September 18 both shoulders were involved by pain and stiffness. On October 22 the patient was unable to work because of loss of strength in holding his hammer and there was painful swelling of his left wrist and fingers and left knee. Then he took to his bed. Two weeks later his hands, wrists, elbows, shoulders, knees, ankles and feet were swollen and painful. At this time, two months after his first symptom, he noted subcutaneous nodules about both elbows. He had lost his appetite and 20 pounds in weight. The patient denied any previous infection.

*Physical Examination*—The temperature was normal in the morning and rose regularly to 100° to 101° F in the afternoon. The pulse was 88 and respiration 20. The patient was apprehensive, in moderate distress and lying motionless in bed. The skin was loose. Examination of the eyes, ears, nose and throat revealed no deformities or infection. There was marked general

ized lymph gland enlargement. The heart and lungs were normal. The blood pressure was 140/80. Abdomen revealed no palpable liver, spleen, tenderness or masses. The genitalia were normal. Rectal examination revealed good

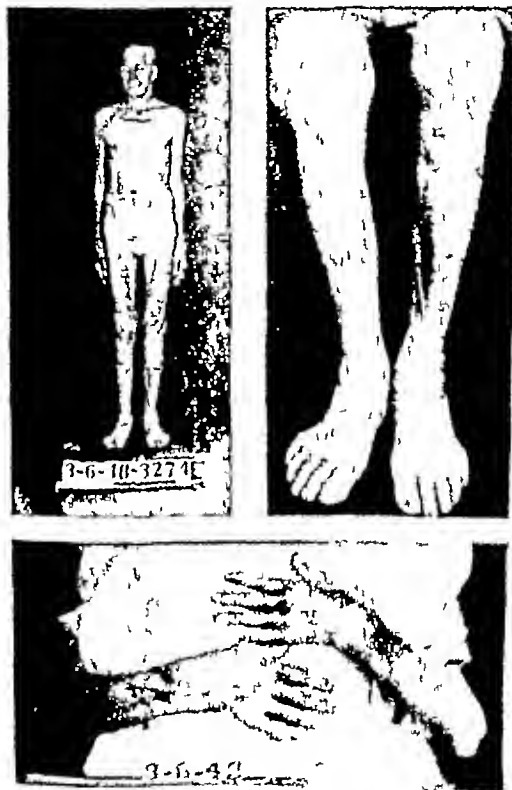


Fig. 1

*Laboratory Examination*—Laboratory studies revealed an anemia of from 11.7 to 12.6 gm of hemoglobin, with a red blood cell count of 4,200,000 to 4,700,000. The white blood count was between 9800 and 21,600 with from 69 to 85 per cent polymorphonuclear leukocytes and as many as 20 per cent young forms. Kidney function test with phenolsulphonphthalein was normal. Repeated routine urine analyses revealed no abnormalities. The erythrocyte sedimentation index was very high and varied from 1.95 to 2.25 mm. per minute. Bromsulfalein excretion was decreased to 22 per cent in forty minutes, using a test dose of 5 mg per kilogram of body weight. The icteric index was 5. Urinary creatine in twenty-four hours was between 560 and 611 mg, probably elevated due to fever and muscle wasting. The fasting blood sugar was 88 mg per 100 cc and the nonprotein nitrogen was 29 mg per 100 cc. The Hinton serologic reaction was negative. A sputum culture and examination revealed no beta streptococci or tuberculosis organisms. A beta streptococcus protein extract revealed no hypersensitivity of the skin to this organism. The total serum protein was 5.6 gm per 100 cc, with a lowering of the albumin to 2.5 gm per 100 cc and a relative hyperglobulinemia of 3.1 gm per 100 cc.

Roentgenograms showed on admission no bony changes but soft tissue swelling about the involved joints. Changes in the texture of the bones are not present early in the course of rheumatoid arthritis.

*Course in the Hospital*—On complete bed rest (including the important bed exercises and plastic resting shells for the involved joints), high protein diet, 3.6 gm of aspirin daily, ½ ounce of Valentine's crude liver extract three times daily, ¼ pound of raw liver daily and a multivitamin capsule three times a day the downhill course of the case was gradually halted. Hot fomentations and hot paraffin wax dips were used respectively to the joints and hands. In two months the temperature chart returned to normal and the increasing weight loss stopped after a total loss of 36 pounds.

Now, at the end of two more months, the patient is allowed to stand for a few minutes daily, he has gained a few pounds and his joint pain has markedly diminished.

*Summary*—This case history of rheumatoid arthritis illustrates the possible fulminating character of the disease. Etiologic factors are distinct only by their complete absence. There is anemia, fever, leukocytosis, weight loss, faulty liver function, disturbed protein metabolism and creatinuria.

The rapid downhill course of the disease has been checked by conservative simple physiologically sound therapy. The tremendous problems of producing further subsidence of the disease and eventual rehabilitation of the patient still exist.

First we will consider the treatment of the inflammatory reaction about the joints and in other parts of the body.

## BED REST

## Including Bed Exercises and Plaster Resting Shells

*Whenever possible* the ideal for a patient with rheumatoid arthritis is to be at complete bed rest. If this is impossible because of economic conditions, as much rest as possible must be instituted. We reach this latter goal by insisting on the patient getting twelve hours in bed each night and by going to bed on week ends, vacations and holidays.

A phrase, abuse of rest has been bandied about with the contention that bed rest produces contractures of the joints and general debility. These criticisms are valid if only bed rest is used without an adequate program of positions and exercises. These latter procedures contribute to the maintenance of joint motion and muscular tone. The program of these essentials as used at the Robert Breck Brigham Hospital is outlined. The positions and postural exercises are done three times a day and the individual joint activities are carried out from five to twenty times, twice a day.

## BODY MECHANICS AND EXERCISES

*Recumbent*

- 1 Lying on back knees bent hands on top of head chin in. Inhale raising chest. Keep chest high and exhale partially.
- 2 Same position. Contract low abdominal muscles, pulling inward and upward.
- 3 Same position. Tilt pelvis backward by contracting low abdominal and gluteal muscles.
- 4 Same position. Lift ribs upward and outward on one side. Relax. Alternate sides.
- 5 Lying with legs flat hands on lower ribs. Inhale spreading ribs laterally. Keep ribs out and exhale partially.
- 6 Lying flat. Tighten quadriceps for full extension of knees.

*Sitting*

- 1 Back flat head erect with chin in hands on hips. Diaphragmatic breathing same as in lying down position.
- 2 Hands on head. Low abdominal contraction as before.
- 3 Hands on head. Rib elevation as before.
- 4 Hands on head. Twist to alternate sides keeping low abdomen flat.
- 5 Hands on head. Bend to alternate sides, in upper part of back keeping low abdomen flat.

*Standing*

- 1 Heels 4 inches from wall feet parallel with weight on outer borders buttocks shoulder blades, head touching wall chin in hands on hips. Diaphragmatic breathing.
- 2 Same position. Low abdominal contraction.

- 3 Same position Pelvic tilt
- 4 Hands on top of head Rib elevation as before.
- 5 Free standing, weight on outer border of feet, low abdomen and back flat, chest forward, head up, chin in, one hand behind neck, other at side Bend, in upper back, to side of lower hand
- 6 Same position, arms at sides Raise arms forward and upward, rise on toes inhaling Lower arms sideways and downward, lower heels, ex haling When used for patients with Strumpell Marie disease the recumbent exercises should all be done with legs extended, modifying this position only when hip/knee flexion deformities or spasm are present

#### EXERCISES FOR SPECIAL JOINTS

These are usually started with the patient lying in bed, or on a plinth, if muscle spasm is present active motion is to be produced in the weak group, with passive or assistive motion returning the part

##### *Shoulder*

- 1 Arm at side, elbow extended Raise arm sideways and upward away from body, until upper arm touches head
- 2 Elbow bent at right angle and on level with shoulder joint, forearm pointed toward ceiling Aim thumb back toward mattress, rotating upper arm outward at shoulder joint.

##### *Elbow*

- 1 Arm at side, palm up Flex and extend elbow joint

##### *Forearm*

- 1 Arm at side, elbow extended Supinate and pronate forearm

##### *Wrist*

- 1 Dorsiflexion and palmar flexion
- 2 Radial flexion and ulnar flexion

##### *Fingers*

- 1 Flexion and extension of metacarpal, proximal and distal interphalangeal joints
- 2 Opposition of thumb
- 3 Touching tip of thumb to each fingertip
- 4 Squeezing of a sponge with fingers and thumb

##### *Hips*

- 1 Legs extended, gluteal contraction
- 2 Legs extended, inward rotation
- 3 Legs extended, abduction and adduction
- 4 Straight leg raising other knee and hip flexed
- 5 Prone lying, pelvis fixed by pillow placed under abdomen, toes over edge of mattress Straight leg raising backward

##### *Knees*

- 1 Flexion and extension, other knee and hip flexed
- 2 Straight leg raising, other knee and hip flexed

##### *Hips and Knees*

- 1 Single bicycle motion, other knee and hip flexed
- 2 Double bicycle motion, other knee and hip flexed



ably is in any progressive systemic inflammatory disorder, and hence a moderately increased amount of vitamins, proteins, fats and carbohydrates, iron, calcium and other dietary substances can be given with benefit to the patient. Since each year the chemists and nutritionists delineate *new* essential food factors previously unknown or unrecognized, it is our opinion that natural food sources are more to be desired than synthetic chemical combinations. When the patient cannot eat because of the large number of vitamin pills he is taking, the therapeutic program is misguided. When clinical syndromes of specific deficiencies are present, we prefer the use of the specific substance *plus* crude food concentrates such as liver extract, cod liver oil and protein hydrolysates. We do not use vitamin D and/or Ertron in the treatment of rheumatoid arthritis because large amounts are dangerous and of no proven value.

Before leaving the subject of nutrition, I should like to mention our recent experience with raw liver therapy in amyloidosis occurring in patients with rheumatoid arthritis. Rarely a patient with amyloidosis and rheumatoid arthritis survives and loses his amyloid disease spontaneously. We have seen only one such case—that of a 16 year old boy who had both diseases, and whose amyloidosis disappeared when he went into a spontaneous remission of his rheumatoid arthritis. Recently we have seen three consecutive patients with this fatal combination lose their amyloid disease when taking one-quarter to one-half pound of raw liver daily. The liver is prepared by grinding it through a fine meat chopper and pressing it through a sieve. It is then taken in one dose between meals in one-half a glass of ginger ale, tomato juice or grapefruit juice. Liver products of various kinds have been used by others with some success in amyloidosis secondary to other conditions. Raw liver therapy in uncomplicated rheumatoid arthritis is being tried with no definite results as yet.

#### MEDICAL THERAPY

Penicillin, streptomycin, neostigmine (Prostigmin) and antitumoral cytotoxic serum, to mention a few of the recent substances under survey, do not alter the course of rheumatoid arthritis.

Salicylates are of value in rheumatoid arthritis because they relieve pain, and relief of pain prevents further muscle spasm and deformity. It has been suggested that salicylates may actually decrease the amount of inflammatory tissue about joints. This has not been proved. We give 0.6 to 0.9 gm. of sodium salicylate or acetyl salicylic acid every four hours during the active stages of the disease.

A mild anemia, probably related to faulty hemoglobin production,

is often present. For this we prescribe 0.3 gms of ferrous sulfate twice a day between meals

No other drug is of routine value in rheumatoid arthritis and it might be well to repeat Hensch's truism—that musculoskeletal pain that requires narcotics is not arthritis. Demerol or morphine derivatives should never be prescribed to a patient with rheumatoid arthritis.

**Gold Therapy**—The use of any drug which can alter favorably the course and outcome of rheumatoid arthritis is justified. Chrysotherapy has been in use twenty years and opinions are still being expressed pro<sup>1</sup> and con<sup>10</sup> by excellent observers. Its exact value is still undetermined. My opinion is that it does alter favorably the course of rheumatoid arthritis, that it is dangerous, that it should be used only after more fundamental approaches to the individual patient's therapy have been found wanting. The toxic manifestations of gold salts are alarming, dangerous and certainly disquieting to the patient and the physician. On the usual dosage outlined below, there are minor toxic effects such as pruritus, rash, stomatitis, definite albuminuria, abdominal pain, definite leukopenia or thrombocytopenia in 10 to 20 per cent of the patients. About 10 per cent will not tolerate the drug and the mortality in large groups of collected series varies from 0.25 to 0.45 per cent.

An important aspect of gold salt therapy which might bring the protagonists and the antagonists of this treatment closer together is to realize that the effect of gold is not to produce a permanent cure but to produce a remission which lasts, as pointed out by Ragan and Tyson<sup>2</sup> from one to fifty-eight months in 75 per cent of their cases. A natural sequel to these observations has been the institution of maintenance dose schedules following the initial course of therapy.

**Preparation**—I have used and found satisfactory Myochrysine (Merck and Co.) and Solganol B Oleosum (Schering Corp.) both of which contain 50 per cent gold by weight.

**Selection of Patient**—It is important to institute therapy before irreversible joint damage has occurred, as no therapy will replace damaged cartilage, bone or periarticular structures. On the other hand, the patient should not be treated with gold preparations until the routine therapy of known value<sup>11</sup> has been instituted for three to six months. Then, if progress is unsatisfactory, gold salt therapy is instituted. Since the repair of badly damaged joints is the province of the orthopedic surgeon and not reparable by medical measures, I feel that individuals young in their disease even if chronologically old are the optimum group to treat. Cessation of progression of damage to the joints may be brought about by gold but certainly the effect is less dramatic and of



less value in the chronic rheumatoid cripple. Since the toxic effects of gold seem to be both that of a heavy metal and idiosyncratic in character the survey of the patient before treatment should include a careful history of previous heavy metal exposure, kidney or liver disease, blood dyscrasias, skin sensitivities and other allergies. We do a urine concentration test, routine urinalysis, complete blood count and a platelet count before starting treatment. If there is any doubt we do not give the patient gold.

*Dosage Schedule (Using Either of the Above Products)*

First week	10 mg
Second week	25 mg
Third to twenty second week	50 mg
Stop one month	
Then every two or three weeks for an indefinite period	50 mg

*The Development of Danger Signs*—Itching, a rash, stomatitis, 2+ albuminuria, abdominal pain, significant leukopenia or thrombocytopenia calls for a halt in therapy and a careful survey of the new complication. It is the general consensus of opinion that when this sign or symptom has subsided a careful smaller dosage may be reinstated. A routine urinalysis, complete blood and platelet count is done every two or three weeks. The patient is questioned at each visit concerning the above subjective signs or symptoms.

In competent careful hands, the course of rheumatoid arthritis in the average case is altered favorably by gold salt therapy. Three series of my patients receiving (1) 200 mg weekly, (2) 50 mg weekly and (3) 25 mg weekly have convinced me that the first is too dangerous a dose and the third dose is ineffective. Our only fatality was in the first series and was due to exfoliative dermatitis and thrombocytopenia purpura resulting in a fatal cerebral hemorrhage.

A new compound, BAL (British Anti Lewisite) (2,3-dimercaptopropanol), has proved useful in counteracting the toxic reactions resulting from gold salt therapy.<sup>12</sup> It has been suggested that the heavy metals such as arsenic, mercury or gold interfere with cellular metabolism and that by the administration of BAL these substances can be removed from the tissues, before or after in vivo linkage with living tissues. There is considerable experimental evidence accumulating that this is as true of gold salts as of arsenicals and mercury. Clinically the earlier BAL is used the more effective it will be in getting rid of the heavy metal effect. BAL is given by injection in a 0.15 gm dose. It is given at first four to six times a day and then reduced in two or three days to one or two doses a day. The results with BAL have included subsidence of exfoliative dermatitis, disappearance of thrombocy-

topenic purpura, and granulocytopenia and improvement in other signs of gold toxicity. However it is well to emphasize at this point that long standing complications of chrysotherapy do not respond to BAL therapy and it is incumbent upon physicians to not unduly or prematurely become careless with gold salt therapy.

## SUMMARY

Until a therapeutic specific for rheumatoid arthritis is found which will produce cessation of activity and a disappearance of subjective and objective manifestations of the disease we must rely upon the above proven valuable plan of treatment in the handling of this difficult clinical problem. The above program warrants an optimistic attitude on the part of the patient and the physician as to the eventual outcome of the problem at hand.

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# THE TREATMENT OF ALLERGIC DISEASES

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The antihistaminic drugs of which benadryl pyribenzamine and neo-antergen are the best known have greatly stimulated the search for chemical agents suitable for the treatment of allergic conditions. Many new drugs will be offered to the medical profession and the methods of treatment now in vogue will certainly undergo changes. However the fact remains that the treatment of patients today depends on the intelligent use of agents, most of which have long been familiar to the practicing physician. An attempt will be made here to outline the general principles of treatment and to indicate how those agents of most value may be administered with greatest benefit and least discomfort.

## HAY FEVER

Management of hay fever consists in avoidance of the offending allergen or treatment with extracts thereof and when necessary the administration of an antihistaminic drug. The antihistaminic drugs alone cannot be depended upon to give adequate relief in more than a small proportion of cases. Patients often say that benefit is marked at first but diminishes after a few days, even though the dosage of the antihistaminic drug is increased. Variations in the intensity of exposure to pollens or other allergens may be one factor. In any case best results are obtained with injection therapy combined with an antihistaminic drug given at the time symptoms occur.

Successful *injection treatment* depends on knowing the cause of the patient's symptoms. Common causes of seasonal hay fever are pollens of grass, wind pollinated trees and weeds and spores from a number of molds which grow on dying or decaying vegetation. Animal danders, house dust and other air borne agents may cause sporadic or continuous symptoms. Foods, in my opinion, are not a common cause of nasal symptoms. The cause can usually be established without difficulty by history combined with *skin tests* done with a suitable technic and with extracts of known allergenic activity. Though basically simple the

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interpretation of history and skin tests requires experience and judgment and it is always necessary to proceed with caution in skin testing. Therefore, this part of the management of the hay fever subject is often turned over to a specialist who can advise as to which extracts, if any, are to be used for treatment and in what dosage. Biweekly subcutaneous injections of allergenic extracts of increasing strength and volume are made until 0.2 to 0.5 cc of a 1:100 or a 1:20 extract has been given. About three months is required for a course of treatment, which should be near completion at the time exposure is considered likely. The manner in which the strength of extracts is commonly indicated is shown in Table 1.

TABLE 1

VARIOUS METHODS OF INDICATING THE STRENGTH OF ALLERGENIC EXTRACTS

Dilution Dry Weight of Pollen in Extracting Fluid	Total Nitrogen mg /cc	Protein Nitrogen mg /cc	Pollen (Noon) Units	Protein Nitrogen (Cooke) units
1 : 20	0.5	0.2	40,000	20,000

Approximate values for an extract made with 1 gm of pollen in 20 cc. of extracting fluid

*Constitutional reactions* are an ever-present hazard during injection treatment and their nature and treatment should be clearly understood by anyone planning to administer allergenic extracts. Such reactions tend to occur in patients exhibiting high degrees of skin sensitivity who are receiving the larger doses of pollen extract and who develop long standing tissue reactions at the site of injections. The inadvertent intravenous injection of an extract is also an important cause.

Constitutional reactions may be guarded against by the following measures

1. Injections should be given at intervals of seven days or less.
2. A dose of extract should be given which is no larger than twice that given on a previous occasion. If large local reactions occur, the dose should be diminished or repeated.
3. The injection site should be in an extremity so that a tourniquet may be applied to delay absorption if necessary. The lower portion of the outer aspect of the upper arm is satisfactory.
4. The plunger of the syringe should be drawn back and held for a few seconds after the needle has been inserted in order to make sure

that a vein has not been entered. If blood appears in the syringe the needle should be withdrawn and inserted elsewhere and the procedure repeated.

5 The patient should remain at the office for thirty minutes after the injection so that prompt treatment can be instituted if a reaction occurs.

The manifestations of a constitutional reaction include the following: itching of the eyes, throat and skin, sneezing, cough, urticaria, wheezing (in asthmatic individuals), abdominal cramps, and weakness. These symptoms usually develop within thirty minutes, although occasionally they develop within a minute or so. (Apprehensive patients may develop weakness, pallor, ringing in the ears, sweating and bradycardia following injections. Such reactions are not allergic in nature and are best treated by having the patient lie down for ten or fifteen minutes.) Ephedrine is effective for the treatment of mild constitutional reactions when taken by mouth at the time symptoms begin in a dose of 25 mg. with or without a barbiturate. More severe attacks should be treated as follows:

1. A tourniquet should be applied proximal to the injected site.
2. Ice or some large cold object from the refrigerator should be applied to the injected site.
3. A small dose of adrenalin 1:1000 (0.1 cc.) should be injected into the site. These measures will delay absorption.
4. Three tenths to 0.5 cc. of adrenalin 1:1000 should be injected subcutaneously in the opposite arm or elsewhere.

After a few minutes the tourniquet may be released and reapplied if symptoms recur. The routine administration of an antihistamine drug, or the incorporation of adrenalin with the pollen extract as a means of preventing constitutional reactions is not recommended as the feeling of security afforded may lead to the administration of dangerously large doses of pollen without the appearance of warning symptoms which would otherwise occur with the smaller doses.

Continuous symptoms of hay fever throughout the year are sometimes seen for which there appears to be no allergic cause. In the absence of nasal polyps or other structural change which may give rise to nasal symptoms one must rely on nose drops, the antihistamine and other drugs by mouth.

Nose drops are applied with a dropper or atomizer in order to shrink edematous mucous membranes causing nasal obstruction. Neo-synephrin in a concentration of 0.5 to 1.0 per cent or Privine in a concen-

tration of 0.025 to 0.05 per cent are effective temporarily. When used in dilute solutions these drugs are well tolerated. Stronger solutions may lead to progressively more rapid return of nasal obstruction, when used over long periods, and may cause symptoms more intense than those for which the medication was originally taken.

*Ephedrine* may relieve symptoms of hay fever and may be taken in the same manner as for asthma (see below). *Atropine* in doses of 0.5 or 0.25 mg by mouth may also afford relief.

The *antihistaminic drugs* are very effective for the relief of hay fever. Patients vary widely in the extent to which side-effects interfere with the administration of these drugs and also the dosage required for relief of symptoms.

Dosages of Benadryl (Parke Davis) and Pyribenzamine (Ciba) for relief of continuous symptoms are shown in Table 2. Neoantergan

TABLE 2

DOSAGE OF BENADRYL AND PYRIBENZAMINE IN ADULTS

	Benadryl	Pyribenzamine
Usual dose	50 mg 4 i. d.	
Maximum dose ordinarily tolerated	50 mg every 3 hours	100 mg every 2-3 hours *
Minimum dose ordinarily effective	20-30 mg 3 i. d.	

(Merck), Antistine (Ciba), Thephorin (Hoffman-La Roche) and Trimeton (Schering) are some of the other antihistaminic drugs which appear to be effective in the treatment of hay fever. Patients should be warned of the possible occurrence of side effects which include drowsiness, a feeling of fatigue, weakness or lassitude, nausea and vomiting and diarrhea. Sleeplessness or nervousness may occur with certain antihistaminic drugs especially Thephorin. Serious toxic reactions are very rare. A single instance of agranulocytosis apparently caused by pyribenzamine has been reported.<sup>1</sup> The drowsiness may interfere with the patient's skill and attention and this should be kept in mind when prescribing antihistaminic drugs for those engaged in driving automobiles, running machinery and similar occupations.

### ASTHMA

Attacks of asthma of a seasonal nature caused by pollens and mold spores can be diagnosed with the aid of history and skin tests and treated by injections, exactly as hay fever. The problem in asthma is to

determine to what extent allergic factors are present and to eliminate causative agents or treat with extracts thereof *Inhalants* (pollens, mold spores, animal danders and house dust) are the chief allergic causes of asthma. The role of *foods* in the causation of allergic symptoms including asthma, is a matter concerning which there is great division of opinion. Foods are, in my opinion, an uncommon cause in adults and furthermore I believe that a food which causes asthma is usually recognized by the patient. There is general agreement that *skin tests* are of little value here and that diagnosis must rest on history, the results of elimination diets and the effect of adding one food at a time to a carefully controlled diet. The subject is complex and requires persistence and the intelligent cooperation of the patient.

Where allergic factors appear to be absent or fail to account for all the patient's asthmatic attacks, a great deal of reliance must necessarily be placed on the alleviation of symptoms with drugs. Mild attacks are readily treated with an *ephedrine* preparation given by mouth in a dose of 25 mg. This may be given alone or in combination with a barbiturate in order to lessen the nervousness frequently caused by ephedrine. Relief of symptoms will usually occur in fifteen to twenty minutes and may last for several hours. The inclusion of aminophylline in oral preparations for the relief of asthma is of doubtful value and may cause nausea.

Mild attacks are usually quickly relieved by inhalation of *epinephrine* 1:100 or proprietary solutions containing epinephrine in higher concentration from a suitably designed nebulizer. Usually five to ten deep inhalations will give prompt relief. *Isuprel*\* in a concentration of 1:200 may be administered in the same manner and appears to be the most effective agent available for self medication. *Isuprel* is likewise available as sublingual tablets. Although effective in relieving mild asthma, our experience has led us to the conclusion that other agents such as ephedrine or sprays of epinephrine or *Isuprel* are preferable.

*Aminophylline* may cause a number of disagreeable side-effects. The drug is relatively ineffective when taken by mouth and often causes nausea. Given as a suppository in doses of 0.5 to 1 gm. by rectum or in similar amounts as a powder in 30 to 100 cc. of water or saline, aminophylline may produce local irritation and occasionally nausea. In most instances, ephedrine or epinephrine will give equal or greater relief and therefore aminophylline by rectum is recommended chiefly when these drugs produce excessive nervousness or palpitation. Intramuscular injections of aminophylline in doses of 0.5 gm. in a volume of 2 cc.

\* 1- $\beta$ -(4-Dihydroxyphenyl)-2-Isopropyl-aminoethanol Winthrop Stearns Co.



may be given deep in the gluteal muscle. Here again, its effectiveness is not great and the indications are limited. Given *intravenously*, in doses of 0.25 to 0.5 gm. in a volume of 10 or 20 cc., aminophylline is the most effective single agent for the treatment of severe asthma. Great care should be exercised to avoid making the injection outside the vein and the solution should be given sufficiently slowly (five to ten minutes) so that few side effects occur. These are tachypnea, taste in the mouth, flushing, tachycardia, palpitation, dizziness, nausea and vomiting. Patients differ markedly in the intensity of side-effects produced by aminophylline.

The combination of intravenously injected aminophylline with the intramuscular injection of 50 or 100 mg. of *demerol* is often effective in relieving asthma. However, the development of severe nausea makes the use of this combination inadvisable in some patients. More prolonged effects can often be produced by giving a combination of drugs in a large volume by continuous intravenous infusion. The following solution has been found valuable:

1 gm. aminophylline (four 0.25 gm. ampules)  
1 cc. epinephrine 1:1000  
100 mg. demerol  
500-1000 cc. saline with 5 per cent glucose

The amounts of the first three items may be modified according to the patient's known tolerance for these drugs. The solution should be given over a period of two to three hours and the infusion should be stopped if side-effects become marked.

*Sedatives* may be given in doses sufficient to permit some rest, but should not be given in doses large enough to cause deep sleep in patients suffering a severe attack of asthma. During the attack, nothing should be done to interfere with the effort to breathe and to cough up the tenacious mucus that forms so prominent a feature of severe asthma. Barbiturates and demerol are valuable, the latter often having a direct beneficial action on the asthmatic attack. Morphine is contraindicated. Ether and oil by rectum is used more for its direct effect on the attack rather than as a sedative. The hazards of heavy sedation should always be kept in mind as well as the realization that the patient with severe asthma will sleep soundly without any sedation whatsoever once the attack is relieved.

*Expectorants* may be given to render the bronchial secretion less tenacious, but they should not be relied on in themselves to relieve asthmatic attacks.

Operative procedures have been advocated from time to time for

the treatment of recurrent or intractable bronchial asthma but these cannot be recommended at the present time

### ECZEMA

The degree to which eczema, both infantile and adult is caused by sensitivity to foods or to substances in the environment is extremely difficult to determine. All traces of foods known to aggravate the skin rash should be *entirely* eliminated from the diet. Direct treatment of the skin with suitable preparations or x ray treatment according to accepted dermatologic practice should be instituted in most cases. Selected cases are benefited by psychotherapy. An antihistaminic drug given by mouth may alleviate itching, but these drugs are not curative. Pyribenzamine ointment may alleviate itching more effectively but it is well to remember that the 2 per cent ointment commonly used may occasionally cause irritation of the skin. Infants with eczema often recover spontaneously at three to four years of age.

### URTICARIA

Three kinds of urticaria may be recognized clinically. Individuals who are *allergic* to certain foods may develop urticaria after eating them. High degrees of allergy are usually present the patient often recognizes the cause of the attacks and the symptoms cease when the offending substance is eliminated from the diet. Frequently marked gastrointestinal symptoms asthma and rhinitis accompany such attacks. Epinephrine, or an antihistaminic drug, given as prescribed below will give relief but symptoms usually last only a few hours or a day or so and subside spontaneously.

*Acute idiopathic urticaria* is a condition unassociated with other allergic conditions as a rule, usually lasts for a few hours to a few days and then disappears spontaneously. Treatment consists in the administration of an antihistaminic drug as described for hay fever or epinephrine subcutaneously as described for asthma. Ephedrine by mouth is usually ineffective.

*Chronic idiopathic urticaria* frequently constitutes a difficult therapeutic problem. Recurrent hives may persist for months or even years. An allergic cause can rarely be demonstrated and treatment is largely symptomatic. Selected cases may improve with psychotherapy. With the exception of urticaria these patients appear to be in good health. An antihistaminic drug given in the manner described for hay fever may give complete or partial relief. Subcutaneous injections of epinephrine in doses of 0.3 to 0.7 cc. of the 1:1000 solution at intervals of three to four hours as necessary is often the best therapy. The more prolonged

action of adrenalin in oil 1 500 two or three times in twenty-four hours may be more satisfactory but care should be taken to avoid overdosage

#### SUMMARY

The recognition of allergic factors causing hay fever, asthma, eczema and hives may require the assistance of the specialist in allergy. A proportion of patients can be satisfactorily treated by avoidance of offending agents or treatment with extracts thereof. In many instances, however, relief of symptoms will depend on therapy with drugs, many of which are very effective in the treatment of allergic disease.

#### REFERENCE

- 1 Blanton W B and Owens, M E B Jr Granulocytopenia Due Probably to "Pyribenzamine" J.A.M.A. 134 454 (May 31) 1947

## DIAGNOSIS AND TREATMENT OF POLIOMYELITIS

LOUIS WEINSTEIN M D PH D \*

The fear often approaching panic, which greets the appearance of acute anterior poliomyelitis in a community necessitates a clear and unemotional approach to the problems of the diagnosis treatment and public health management of this disease. The hysteria of the laity is often transmitted to physicians and there is a tendency to suspect this infection of the nervous system in many instances where there is little to support such a suspicion. Because of the lack of specific diagnostic tests the presence of any of the many symptoms or signs of poliomyelitis may lead to the erroneous diagnosis of this disease in many individuals particularly in young children if they develop nonspecific illnesses in the months of May through October. Such mistakes lead to much unnecessary emotional distress in many patients or their parents and careful judgment must be exercised in situations which do not present clear-cut evidence of infantile paralysis.

Nevertheless this infection must be kept in mind at all times since it may occur sporadically in all months of the year it is commonest however during the summer and early fall. The diagnosis of poliomyelitis can usually be established on the basis of the combined information obtained from an epidemiologic, clinical and laboratory study of most cases, but even with these aids, many instances particularly those of the abortive type will be missed. It is important to stress that in not a small number of cases the final opinion can be arrived at only after following the course of the illness for some time.

Like all diseases for which no specific therapeutic agent is available poliomyelitis has been treated in a great variety of ways. Great differences in opinion have always existed concerning the proper treatment of this infection. The many radical changes which therapy has undergone in the last twenty five years reflects the varied interests of the physicians under whose care patients came during the acute phase of the illness. There is disagreement even today among members of the various medical specialties as to the methods of treatment which yield the best results. It is impossible to lay down rigid rules for the therapy.

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of infantile paralysis, time and experience with some regimens have frequently proved their complete lack of value in spite of the enthusiasm of their advocates. It is important to choose certain procedures and use them, without bias, long enough to determine their true worth.

Indeed, the problem of the treatment of poliomyelitis is so complex and so variable, depending on the type and stage of neuromuscular involvement, that the combined efforts of the internist, pediatrician, psychiatrist, orthopedist, physical therapist, public health official, social service worker and occupational therapist are necessary to produce the maximum of good results. It cannot be stressed too strongly that the victim of paralytic poliomyelitis who survives needs not only to have his affected nervous system and muscles treated, but requires vigorous therapy for the psychic and social disruptions which often are remote results of this disease, the enthusiasm directed towards improvement of neuromuscular function must never overshadow the effort to treat the patient as a whole.

#### DIAGNOSIS OF POLIOMYELITIS

The diagnosis of poliomyelitis often depends on information derived from the study of the epidemiologic, clinical and laboratory features of any case. Although in many cases the course of the illness, the physical findings and laboratory data are sufficient to incriminate or eliminate infantile paralysis, in some instances this cannot be done without the help of epidemiologic information. Poliomyelitis is primarily a disease of the summer and early fall, May through October, although sporadic cases may occur at any time of the year. Although poliomyelitis is considered primarily a disease of very young children, Burnet<sup>8</sup> and others have pointed out that there has been a shift in the age incidence in many parts of the world. Whereas in the past the great preponderance of cases occurred in the age group 2 to 6, with 90 to 95 per cent being under the age of 10, there has recently been a large increase in the number of individuals aged 10 to 15 years and in adults.

Infantile paralysis is still, however, primarily a disease of childhood and adolescence. The absence of other viral infections of the nervous system such as equine encephalomyelitis, mumps encephalitis or Japanese B encephalitis in a community eliminates these diseases as confusing issues. Lack of contact with rubeola, rubella, variola and varicella or absence of a recent attack of these exanthemas will rule out postinfectious encephalomyelitis. Complete reliance on epidemiologic

data may, however, lead to error since the first few cases of a virus infection of the nervous system other than poliomyelitis may go unrecognized. The presence of a proved attack of poliomyelitis in a household is frequently helpful in making a decision concerning the etiology of disease of the nervous system in another person in the same family.

A careful study of the clinical course of the disease is frequently of aid in establishing the diagnosis of poliomyelitis. The incubation period is between three and thirty six days (Horstman<sup>14</sup>). A history of contact with a known case is often difficult to obtain. Most patients have prodromal manifestations for from one to four days before signs of involvement of the central nervous system become apparent. In some instances there is no prodrome and the disease starts suddenly with signs of meningeal irritation and/or paralysis. The prodrome may be of two types: one in which gastrointestinal manifestations are present and the other characterized by the signs of an upper respiratory tract infection. Fever, nausea and vomiting usually with constipation—diarrhea is uncommon (Horstman<sup>14</sup>)—or fever with slight sore throat but with marked redness of the pharyngeal mucous membrane (Horstman<sup>14</sup>) constitute the important symptoms in the two kinds of prodromes. The fever is usually of mild degree. In some cases the erroneously labeled dromedary type of temperature elevation may be present: that is, a moderate fever during the prodromal period followed by defervescence for a day or more and then a secondary rise in temperature as signs of involvement of the nervous system become apparent. In the prodrome as well as in the early phase of the manifest disease generalized lymphadenopathy is common.

The symptoms and signs indicating invasion of the nervous system by the virus are the result of three different mechanisms: (1) Increase in intracranial pressure with headache, nausea and vomiting. (2) Irritation of the meninges resulting in varying degrees of stiffness of the neck and back and spasm of the hamstring muscles—Kernig sign. Stiffness of the back has been called the spine sign and is evidenced by the inability of the patient to get his head between his knees in the sitting position with the legs partially drawn up. (3) Involvement of various portions of the spinal cord and/or brain with the production of varying degrees of paresis and paralysis of muscles whose innervation has been temporarily or permanently damaged. It is important to point out that studies of the pathologic changes in experimental animals and humans dying of poliomyelitis reveal damage in many parts of the nervous system: the concept that this disease in-

only the anterior horn cells in the spinal cord is no longer. A lack of correlation between the clinical and patho-anatomic is not uncommon, however. In patients with abortive or non-c poliomyelitis localizing signs are absent. In the paralytic form of the disease, localizing signs indicating involvement of any part of the spinal cord or the brain stem may be present. In a number of instances, the brain alone may appear to be affected; these patients may or may not show weakness or paralysis of muscle groups and the clinical picture has been referred to as cephalitis. In some cases, there is evidence of involvement of different parts of the nervous system—bulbosplinal or bulboencephalitis—simultaneously. Whether or not cerebellar symptoms in poliomyelitis is not settled, although pathologically the vermis usually shows structural damage.

A helpful sign which is present most often in the paralytic and non-c types of poliomyelitis but which may be elicited occasionally in the abortive form of the disease is *Hoyne's sign*. This is elicited in the patient lying flat on his back by placing the hands beneath the shoulders and lifting up. When the sign is positive the patient's head falls back limply in a position of hyperextension. In the normal individual the head follows along in a plane when the body is raised. The sign, first described by Peabody, Draper and Dochez<sup>21</sup> but called *Hoyne's* name, is not specific for infantile paralysis but may be present in children severely ill with pneumonia or meningitis.

When presented a clinical classification of poliomyelitis which, though not new, may be helpful to the reader in orienting himself with respect to the different clinical forms of the disease

### CLINICAL CLASSIFICATION OF POLIOMYELITIS

Abortive poliomyelitis

Nonparalytic poliomyelitis

Paralytic poliomyelitis

#### 1 Spinal

(a) Cervical

(b) Thoracic

(c) Lumbar

(d) Any combination of a, b, c

#### 2 Bulbar

(a) Upper cranial nerve group involvement—N 3, 4, 5, 6, 7, 8

(b) Lower cranial nerve group involvement—N 9, 10, 11, 12

(c) Autonomic center involvement—respiratory and/or circulatory centers

(1) Respiratory center

(2) Circulatory center

(3) Combination of (1) and (2)

#### 3 Bulbosplinal

## IV Polioencephalitis—paralytic or nonparalytic

- 1 Diffuse encephalitis
- 2 Focal encephalitis
- 3 ? Cerebellar involvement
- 4 Bulbo-encephalitic disease
- 5 Spinal-encephalitic disease.

In many instances, examination of the cerebrospinal fluid provides the decisive information necessary to establish the diagnosis of poliomyelitis. Peabody, Draper and Dochez<sup>21</sup> and many other investigators have shown that the cell count of the spinal fluid is usually highest during the first week of the disease in the preparalytic and paralytic stages at which time mononuclear cells are predominant in a fairly large number of cases; however, neutrophilic leukocytes are most numerous at the beginning of the illness. The protein content of the cerebrospinal fluid is often normal or low in the first week of the infection, rises during the second to the fourth weeks and then decreases gradually, often not returning to normal levels until the tenth week. In about 10 per cent of proved instances of infantile paralysis no increase in cells will be present during the entire course of the disease.

The predominantly lymphocytic pleocytosis of poliomyelitis may cause confusion with other viral and, less commonly, bacterial infections of the nervous system. Later in the course of poliomyelitis the absence of cells with an increasing concentration of protein in the cerebrospinal fluid may lead to an erroneous diagnosis of the Guillain Barré syndrome of infectious polyneuritis. Thus, the presence of abnormal findings in the cerebrospinal fluid is in itself insufficient to establish a definitive diagnosis of infantile paralysis. If the course of the disease and the physical findings are highly suggestive of the presence of poliomyelitis, a positive spinal fluid helps to confirm the diagnosis.

**Abortive Poliomyelitis.**—Abortive poliomyelitis is that type of the disease in which prodromal manifestations are present but there is never any clinical evidence of invasion of the nervous system by the virus. These patients have only a mild gastrointestinal upset or the signs and symptoms of an acute upper respiratory tract infection. Andelman and his co-workers have shown, however, that in many cases of abortive poliomyelitis elevation of the spinal fluid protein above 45 mg. per 100 cc. may be present three to six weeks after the clinical manifestations have disappeared.

There are no specific diagnostic methods for establishing the diagnosis of abortive poliomyelitis. Serologic tests are impractical because of wide antigenic differences in strains of the virus and the difficulty



of infecting small laboratory animals. The season of the year, the presence of poliomyelitis in the community or in the family of the patient, etc., focus attention on mild gastrointestinal or upper respiratory tract symptoms. In the absence of suggestive epidemiologic evidence such mild illnesses are rarely associated with the possibility of infantile paralysis. The number of cases of abortive poliomyelitis far outnumbers the other forms of the disease, probably by ten to twenty times. Wickman,<sup>28</sup> Trask, Vignec and Paul,<sup>29</sup> Casey, Fischbein and Bundesen<sup>4</sup> and Horstman, Ward and Melnick<sup>18</sup> have all shown that cases of the abortive type are just as dangerous to the public health as clinically manifest instances of the disease, since they harbor the virus in their pharyngeal secretions and stools. The vast majority of persons with abortive poliomyelitis are overlooked. The presence of nonspecific symptoms in any member of a household in which a proved case of infantile paralysis has occurred should always arouse the suspicion that such a minor ailment is abortive poliomyelitis and proper steps should be taken to prevent an unusual degree of dissemination of the virus into the community by the suspected individual.

**Nonparalytic Poliomyelitis**—Nonparalytic poliomyelitis is that form of the disease in which there is clinical and/or laboratory evidence of invasion of the central nervous system without evident paresis or paralysis of any of the muscles. It occurs probably four to five times as often as the paralytic type and mild cases may be missed completely. The prodromal manifestations are usually followed by signs of increase in intracranial pressure and meningeal irritation, which may last for from a few days to a week or more and then disappear, leaving no residua. The abdominal and cremasteric reflexes often are absent early in the disease and then return. Some patients who are originally thought to have nonparalytic poliomyelitis may later reveal slight to moderate weakness of various muscle groups, particularly those which support the spinal column; it is not rare, indeed, for varying degrees of scoliosis to appear as long as a year after an individual has recovered from what was thought to be a nonparalytic attack. Although the existence of nonparalytic poliomyelitis may be suspected on the basis of the clinical course and epidemiologic evidence, spinal fluid examination is frequently helpful in confirming the diagnosis.

This infection may be confused with healing bacterial meningitis, lymphocytic choriomeningitis, encephalitis due to toxic agents and other viruses, and meningismus produced by disease outside the nervous system. A carefully taken history, such epidemiologic data as are available, and the clinical course of the illness often help to rule out such causes of neurologic manifestations. In the hands of the most experienced clinicians there doubtless are, however, a small number

of cases in which an incorrect diagnosis is made. As has been pointed out above, isolation of the poliomyelitis virus and serologic studies to demonstrate rising neutralizing antibody titers against it are an impractical approach to the problem of specific recognition of non paralytic poliomyelitis at the moment. This does not mean however that serologic tests are of no value; they may be of great aid in proving that a suspected case is not actually poliomyelitis but due to the virus of mumps, lymphocytic choriomeningitis or other infection. It is helpful, therefore, in cases where a possibility that another virus may be involved exists, to carry out studies designed to demonstrate the presence of the suspected infecting agent. Careful clinical follow up of a patient after he has recovered from the acute phase of the disease may substantiate the diagnosis of nonparalytic poliomyelitis in some instances because paresis of various muscles may appear weeks later and leave no doubt that the original illness was infantile paralysis.

**Paralytic Poliomyelitis—Spinal Type.**—The onset of paralytic poliomyelitis is frequently preceded by the prodromal symptoms described above but marked muscle weakness may appear suddenly without any preceding illness. In some cases a double-humped fever curve—an elevation during the prodrome followed by a secondary rise in temperature concurrent with the onset of paralysis—may be present. The signs of meningeal irritation—stiff neck, stiff back (*spine sign*) and the 'spasm' of the hamstring muscles (*Kernig sign*) and *Hoyne's sign*—are usually found in patients with paralytic poliomyelitis.

In the early stages of the spinal type of the disease patients frequently complain of cramping pain in the muscles innervated by the neurons which have been affected. The pain may be extremely severe and spasm of the involved muscles is often easily detectable. Little if any weakness is demonstrable. In some cases with the onset of nervous system manifestations but paresis and paralysis appear later. In some instances increase in muscle weakness is very slow. In others it develops with moderate rapidity while in a few individuals rapid progression of paralysis occurs and complete involvement of all the muscles of the trunk and extremities may take place in forty-eight hours. Rarely a rapidly ascending paralysis of the Landry type is observed.

The location of the muscular paresis or paralysis depends entirely on the portion of the spinal cord affected by the disease. The three portions of the cord may be involved singly or in any combination. Thus, manifestations of isolated infection of the cervical, thoracic or lumbar

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The word "spasm" is used in quotes throughout this paper since an exact physiologic definition of it in poliomyelitis is not agreed upon. It is used here to denote tightness of muscles with or without pain.

areas may be present or the changes may be due to involvement of any two or all three parts of the spinal cord. The lumbar portion of the cord is the one most frequently affected but cervicolumbar, dorso-lumbar or cervicodorsal involvement is quite common. "Skip areas," with disease of isolated segments of the various divisions of the cord, are common in paralytic poliomyelitis.

In infection of the cervical portion of the spinal cord, there is weakness of the muscles of the shoulders, arms, neck and diaphragm the extent and degree of paresis depending on how widespread the damage in the cervical area is. The radial periosteal, biceps and triceps reflexes may disappear, being absent usually when true paresis or paralysis of the muscles of the arms is present. Fasciculation of the affected shoulder or arm muscles is a frequent finding. When the cervical cord is involved, extreme watchfulness is necessary because the disease not infrequently spreads to involve the brain stem with the production of cranial nerve dysfunction or failure of the respiratory or circulatory regulating mechanisms in the medulla. Weakness or complete paralysis of the diaphragm is manifested by a decrease in the vital capacity. This can be measured crudely by having the patient count at the rate of one count per second after the deepest inspiration. Inability to count beyond 6 to 8 usually is an indication for the immediate use of a mechanical respirator.

When the thoracic portion of the spinal cord is involved, there is a varying degree of weakness of the muscles of the chest, upper portion of the abdomen, and spine. Difficulty in breathing due to paresis or paralysis of the thoracic muscles may also occur and is evident on inspiration when lack of motion of the intercostal musculature is apparent. The muscles of the chest wall may be in "spasm", when the diaphragm is also "spastic" the whole chest may appear rigid and the patient is unable to move the thoracic cage in the face of only minor degrees of weakness of the muscles of respiration. Fasciculation of the thoracic, abdominal or spinal muscles may be present.

Involvement of the lumbar portion of the cord produces weakness of the muscles of the upper and lower legs and lower portions of the abdomen and back. Pain, "spasm" and fasciculation of the affected muscles are present frequently even before paresis or paralysis appears. Although the reflexes in the legs may be elicitable early in the course of the disease decrease in their intensity followed by complete loss occurs as paralysis becomes established. Weakness of the iliopsoas muscles produces inability to sit up from a lying position. There may be marked foot drop and inversion or eversion of the foot, depending on which of the calf muscles are affected. Internal or external rota-

tion of the thigh may be present when the muscles of the hips are weak.

When skip areas of infection in the cord are present or when the whole spinal axis is involved the distribution of muscle weakness or paralysis may be very extensive. Although paralysis of one leg is commonest in paralytic poliomyelitis combinations of paralysis of one leg and one arm both legs, one or both arms or all four extremities are not infrequent. Any of these pareses may be present together with weakness of the thoracic wall and/or the diaphragm paralysis of the respiratory musculature is found most often however when weakness of the upper arm and shoulder muscles are present.

The abdominal and cremasteric reflexes usually disappear before muscle weakness is marked in paralytic poliomyelitis and may be absent during the entire course of the disease. Constipation abdominal cramps and meteorism are common and probably are due to involvement of the autonomic nervous system with partial paralytic ileus as well as weakness of the abdominal muscles which causes difficulty in expulsion of feces. The temperature is usually elevated for the first few days of the disease when it has returned to normal levels and remained there for at least forty-eight hours there is, as a rule, no further extension of paralysis. In a few cases however there may be extensive progression of muscle weakness for days after the fever has disappeared. In a few patients with extensive muscular paralysis there is severe sweating tachycardia and flushing of the skin in those with respiratory muscle paralysis a transient red macular rash most prominent on the skin of the anterior chest, shoulders and abdomen, may appear.

**Bulbar Poliomyelitis.**—Although the incidence of bulbar poliomyelitis was thought to be only about 6 per cent by Wickman<sup>24</sup> recent observations indicate that this form of the disease is quite common in some epidemics the Minnesota Poliomyelitis Research Commission<sup>11</sup> has reported a rate of occurrence of 23 per cent in children under 16 years of age and an even larger number of cases in older patients. The prodromal manifestations and spinal fluid changes of this type of poliomyelitis are the same as those in the nonparalytic and spinal paralytic forms. Spasm of the neck back and hamstring muscles is almost always present. The clinical pictures which are found depend on the portion of the brain stem involved. The term bulbar poliomyelitis is used in this paper in the same sense as that applied to it by the Minnesota Poliomyelitis Commission<sup>11</sup> and denotes involvement of the medulla pons and midbrain. The signs and symptoms which appear result from involvement of (a) the upper cranial nerve group nuclei, (b) the lower cranial nerve group and (c) the respiratory and

circulation regulating centers in the medulla. In addition, combined bulbar and diffuse or focal encephalitic or bulbar plus spinal involvement may occur.

In disease of the upper cranial nerve nuclei, paresis of N 3, 4, 5, 6, 7 and 8 may be present. Isolated ocular nerve palsies, total external ophthalmoplegias, pupillary disturbances, Horner's syndrome, and hippus have been reported in poliomyelitis. There may be unilateral or bilateral paresis or paralysis of the fifth nerve and difficulty in chewing and closing the mouth as well as spontaneous deviation of the jaws on opening the mouth may be present. Paralysis of the facial nerve is quite frequent in bulbar poliomyelitis. This is usually central in character and either the entire face or only the upper or lower parts may be affected. Disturbances of vestibular function and deafness result from involvement of the nucleus of the eighth cranial nerve.

When the nuclei of the lower cranial nerves—9, 10, 11, 12—are affected, the life of the patient may be in great danger, particularly if function of the tenth nerve is impaired since swallowing is controlled by the combined action of N 10, 11 and 12. With involvement of these nerves, the voice has a nasal quality and movement of one or both halves of the soft palate is decreased or absent. Saliva collects in the hypopharynx because of the difficulty in swallowing and not because of excessive secretion. Hoarseness and laryngeal stridor may follow weakness or paralysis of the vocal cords. Unilateral or bilateral weakness of the tongue and paresis or paralysis of the sternocleidomastoid and/or trapezius muscles may be present. The inability to swallow which results from involvement of the tenth nerve leads to pooling of saliva and food in the pharynx with consequent obstruction to the airway. The aspiration of fluid into the larynx, reflex spasm of the glottis, and the possibility of abductor paralysis of the vocal cords all constitute a constant, very serious threat to life. Minor or major pareses of the soft palate and pharyngeal muscles may be detected by having the patient repeat the test phrases "prunes and prisms" or "Kellogg corn krispies," both of which have a highly nasal quality when spoken by individuals with palatal or pharyngeal weakness.

When the medullary respiratory center is affected, there is irregularity of the rhythm and rate of breathing. Respirations are shallow and as the disease progresses, are interrupted by longer and longer periods of apnea until breathing stops completely. The thoracic muscles and diaphragm do not become weak unless spinal involvement is present. Hiccupping is frequently present in the early stages of res-

piratory center dysfunction. The Minnesota Poliomyelitis Commission<sup>17</sup> has pointed out that these symptoms are frequently caused by hypoxia and may be present before the appearance of cyanosis. They urge the use of the Milliken oximeter in the detection of the early hypoxic state. Late in the course of the infection the temperature, pulse rate and blood pressure are elevated but all fall to shock levels terminally. In fatal cases there is increasing cyanosis which fails to respond to the administration of oxygen.

The manifestations of involvement of the circulatory regulating center are a deep cherry red color of the lips, flushed florid appearance of the skin, a very rapid irregular pulse, small pulse pressure when the blood pressure is normal and moderate to severe hypotension. These signs may be present simultaneously with evidence of cranial nerve disease. Hyperthermia, cold mottled clammy skin, shallow respiration and anxiety, restlessness and confusion may appear as the circulatory mechanism becomes progressively more impaired. The heart beat usually stops before cessation of respirations.

**Polio-encephalitis.**—Encephalitic symptoms are seen not infrequently in patients with bulbar poliomyelitis or with no other signs of infantile paralysis except those of meningeal irritation and prodromal manifestations. The incidence of encephalitis varies considerably. An epidemic of infantile paralysis in which a large number of cases of the encephalitic form were present and which was thought to have originated from the ingestion of contaminated milk has been described recently by Goldstein, Hammon and Viets.<sup>18</sup> The manifestations of polio-encephalitis are of two types: those due to diffuse and those resulting from focal involvement of the brain. In the diffuse form, the patients are anxious, apprehensive, have a feeling of impending doom and are plagued by ideas racing through their minds. Quivering, trembling, twitching and jerking of the facial muscles and extremities, flushing of the face, tremor of the hands and extremely rapid movements may all be present. Insomnia may be severe. In fatal cases, confusion may be marked and then progress to lethargy and death. Prolonged somnolence has been seen by us in several cases; one patient was in coma for three days but made a complete recovery. Paralysis of the bladder has been a common finding in the patients with polio-encephalitis admitted to our hospital.

In focal polio-encephalitis there may be objective evidence of brain damage or the lesions may be clinically silent and demonstrable only at necropsy. Visual verbal agnosia, myoclonic jerks, grand mal convulsions which occasionally may persist for a long time after recovery from the acute phase of the disease, spastic hemiparesis, ataxia of one

arm or leg and hydrocephalus have been described as occurring in this form of poliomyelitis

### SUMMARY OF THE DIAGNOSIS OF POLIOMYELITIS

The diagnosis of poliomyelitis is usually made on the basis of an epidemiologic, clinical and laboratory evaluation of a case. The presence of poliomyelitis in the community or, even more important, in the family of a suspected patient is important circumstantial evidence. A prodrome characterized by fever, headache, mild gastrointestinal disturbances or the signs of upper respiratory infection, particularly a red throat, are all highly suggestive of infantile paralysis. The absence of a prodrome, however, does not rule out the possibility of this disease since, in a small number of instances, the onset of paralysis may be sudden and without warning.

Abortive poliomyelitis is the form of the disease in which there is no evidence of involvement of the nervous system in the acute stage and only prodromal manifestations are present. This type of patient constitutes as great a menace to the public health as a clinically evident one since he is capable of disseminating virus in his pharyngeal secretions or feces. In nonparalytic poliomyelitis, the characteristic prodromal features and, in addition, signs of meningeal irritation and frequently loss of the abdominal and cremasteric reflexes as well as abnormalities of the spinal fluid are the common findings. In the paralytic types of the disease, the outstanding feature, in addition to all of the changes present in the nonparalytic form, is evidence of nerve dysfunction with paralysis of various muscle groups. The location of the muscle weakness will depend on the site of the infection in the spinal cord or cranial nerve nuclei. Involvement of the medulla produces marked alterations in function of the respiratory and circulatory regulating mechanisms. Polio encephalitis results in the presence of signs of focal or diffuse disease of the brain.

Space is not available for a complete consideration of the differential diagnosis of poliomyelitis. There are a number of other conditions with which this infection may be confused, these include various affections of muscles, bones or joints, such as trauma, rheumatic fever, trichinosis, osteomyelitis, scurvy, arthritis, diseases of the central nervous system such as subarachnoid hemorrhage or other cerebrovascular accidents, viral and "toxic" encephalitis, healing bacterial meningitis, and acute attacks of multiple sclerosis. Examination of the spinal fluid is often helpful but may be confusing because in about 10 per cent of proved cases of poliomyelitis there are no detectable abnormalities and pathologic changes, when present, may resemble closely those found in

other diseases of the nervous system. Isolation of the virus of infantile paralysis or studies of the neutralizing capacity of the serum of patients are too impractical at present to be useful in clinical practice.

### THE TREATMENT OF POLIOMYELITIS

Poliomyelitis presents a varied group of therapeutic problems none of which can be solved by the application of specific remedies. Therapy in this disease has a number of objectives which must be kept constantly in mind if the maximum degree of recovery and eventual rehabilitation is to be anticipated. In the case of severely ill patients especially those with bulbar or respiratory muscle involvement the first purpose is to save life. In all cases every effort should be made to relieve pain to alleviate muscle spasm to preserve or increase motor function to minimize disability to prevent or correct muscular deformity, and to treat the emotional disturbances which occur so frequently.

The best place to treat an individual with poliomyelitis is in a hospital where he can be isolated properly. Institutions which care for patients with this disease should have available the necessary mechanical equipment (hot pack machines, respirators, walking apparatus, exercise rooms, Hubbard tubs and so forth). Most important is the need for medical and nursing personnel trained in the care and management of infantile paralysis. In many cases the combined efforts of the experienced internist, pediatrician, orthopedist, psychiatrist, nurse, physiotherapist, social worker, and occupational therapist are necessary in treating the illness from the time it starts until rehabilitation, if possible, has been accomplished.

The treatment of poliomyelitis can be divided for purposes of discussion, into that applied during the acute, convalescent and chronic stages. The nature and purpose of therapy vary with the type of poliomyelitis and the phase of the disease. In the discussion to follow emphasis has been placed on the acute stage and only brief mention made concerning treatment later in the illness.

**Abortive Poliomyelitis**—Patients with abortive poliomyelitis usually require no treatment. They should be kept at rest during the period when the gastrointestinal or upper respiratory symptoms are present because considerable clinical evidence is accumulating that exercise and muscular fatigue may predispose the nervous system to invasion by the virus. It is of course impossible to recognize all of the cases of the abortive form of the disease and only those with known family exposures can be suspected and managed properly. Careful watch must be kept for development of signs of meningeal irritation and mild



weakness since a few individuals may have paralytic disease of such minor degree that the manifestations of neurologic involvement may be completely overlooked. If abortive poliomyelitis is suspected strongly the affected person should be isolated since, as has been pointed out above, this type of patient is just as capable of disseminating the infectious agent as is a clinically manifest case.

**Nonparalytic Poliomyelitis**—When the diagnosis of nonparalytic poliomyelitis is made, admission to a hospital is strongly indicated. The patient should be placed in a bed with a wooden board under the mattress since solid support under the back and hips produces relief of the pain in the back. The "spasm" of the muscles of the neck, back and thighs which is frequently present in patients with nonparalytic poliomyelitis is best relieved by the application of heat. Hot wet packs of the type used by Sister Kenny, warm tub baths (104° F [Gurewitsch and O'Neill<sup>11</sup>]), diathermy and the like have all been used successfully by various clinics. The method used to apply heat, while a matter of great controversy at times, seems to be of little importance. In our hospital, hot wet packs prepared in a so called "hot pack machine" (Emerson) are used routinely, they are made of pieces of wool cut to fit the extremities, back or neck of patients of various age groups and are cheap and easily replaceable. The frequency with which heat needs to be used varies with the degree of discomfort present and the length of time over which muscle "spasm" persists. The application of hot packs every three to four hours during the day for from several days to a week relieves pain completely in most patients. In a few cases in which "spasm" is more persistent and severe, treatment must be given more frequently (every fifteen to thirty minutes) for a longer period of time, sometimes as long as two or three weeks.

As important as treatment for relief of discomfort is frequent determination of muscle strength. It is well known that patients who have been thought to have nonparalytic poliomyelitis may later show evidence of varying degrees of paresis. Examination of muscle function two to three times a week in the hospital by persons especially trained in the maneuvers necessary for the detection of minor degrees of weakness is important in directing the attention of physiotherapists and others to the institution of protective and corrective measures early in the course of the disease.

Patients with nonparalytic poliomyelitis may have disturbed bowel function—constipation and flatulence, these are best treated by saline enemas. The patient should be encouraged to move about freely while lying in bed. Fluids are given in quantities sufficient to maintain a normal state of hydration, the diet should not be restricted. There is



well beyond the point of pain after the administration of a relaxing dose of curare. He has expressed the opinion that such treatment leads to earlier rehabilitation. In our hospital stretching has been carried only up to and slightly beyond the point of pain. Curare has not been used but hot packs are employed to decrease muscle spasm. We have been very favorably impressed with the results of this manipulation when carried out once or twice daily in causing the more rapid disappearance of muscular "spasm" and earlier return of complete range of joint movement. The value of such a procedure still requires extensive investigation, however, before it can be recommended, without qualification, as a standard procedure in the treatment of paralytic poliomyelitis. It would appear, however, that the stretching of muscles far beyond the point of pain is not necessary and that equally good results can be produced by less vigorous manipulation. The cooperation of the patient can be maintained much more easily if the treatment is not excruciatingly uncomfortable.

Kabat and Knapp<sup>15</sup> were the first to use *prostigmine* in the treatment of poliomyelitis and found that the drug produced relaxation of muscle "spasm", when large doses were employed, skeletal muscle function was increased but unpleasant parasympathetic symptoms were also present. Examination of the value of prostigmine in the therapy of infantile paralysis in other clinics (Anderson,<sup>2</sup> Fox and Spankus<sup>6</sup>) has led to the conclusion that this agent produced very irregular and unpredictable effects on muscle "spasm" and that it is not very useful in the treatment of this disease.

Ransohoff<sup>22</sup> was first to make a trial of *curare* in the treatment of poliomyelitis and recommended its use together with vigorous physiotherapy. Fox<sup>7</sup> examined the effectiveness of this drug in patients with poliomyelitis and noted that, although a few individuals had subjective improvement, the objective findings were not encouraging. The bulbar type of infection did not respond to this treatment. It was his feeling that, while curare might be of temporary benefit in some instances, it was dangerous and its use in infantile paralysis should not be encouraged. Our own rather limited studies confirm the observations of Fox. In 1947, Ransohoff<sup>23</sup> reported further studies on the value of curare in 29 cases and reaffirmed his early opinion concerning its effectiveness in producing earlier and more complete return of muscle function. The dose of drug employed was 0.9 unit per kilogram of body weight every eight hours for the first twenty-four hours and then 1.5 units per kilogram, if no adverse reaction occurred. Blurring of vision or diplopia was used as criteria of adequate dosage. Opinion on the usefulness of curare in paralytic poliomyelitis is, at the moment,

not completely crystallized further investigation of this agent is indicated. Another drug which relaxes skeletal muscle, Myanesin has had a short trial in the treatment of poliomyelitis, but the number of patients treated thus far is still too small to allow any definite conclusions as to its merit.

Patients with spinal paralytic poliomyelitis who have paresis or paralysis of the muscles of respiration need special treatment. It is very important to determine when respiratory efficiency has decreased to the point where mechanical help is necessary. *Artificial respiration* should never be delayed if possible until cyanosis has appeared because anoxia may have been present long enough to produce irreversible damage to the nervous system. The Milliken oximeter is helpful in determining the degree of oxygenation of the blood. As the normal respiratory mechanism becomes weaker the accessory muscles of breathing become active. Restlessness is marked in the early stages, but as the failure of respiration progresses the exertion of trying to breathe and chronic anoxia lead to rapidly increasing fatigue. It is at this time that a mechanical respirator is often most helpful. Estimation of the vital capacity is a valuable aid in deciding when artificial respiration should be given. A crude evaluation of the vital capacity can be carried out by having the patient take a deep inspiration and then count at the rate of one count per second. Normal persons can count up to between 20 and 30. When the count cannot be carried beyond 6 to 8, the patient should be placed in a mechanical respirator.

The type of respirator used is of little importance; more important is a complete knowledge of the proper operation of a particular machine. All personnel who care for individuals who are placed in respirators should be instructed in the correct methods of management of both the patient and the mechanical device, especially in emergency situations such as may arise when power failures occur. When a patient is put into the respirator a light cotton or flannel bandage is placed around the neck so that the discomfort of the oscillations of the rubber respirator collar which occur with changes in pressure within the machine are minimized. The body should be covered with light blankets, a board placed against the feet to prevent foot drop and the arms arranged in the most comfortable position. The negative pressure used should not exceed  $-16$  cm. of water except in large individuals with heavy chest walls when it may be increased to  $-18$  cm. In young children and in slight female adults negative pressures not in excess of  $-10$  to  $-11$  cm. of water frequently produce adequate respiratory excursions. The respiratory rate is adjusted to be between 12 and 16 per minute.

The fear engendered by the necessity for use of the respirator is overwhelming in many patients and they must always be told what is going to be done before they are placed in the machine. Reassurance as to the chances of survival is often necessary and it is well to stress the importance of the mechanical device in giving the respiratory muscles a rest. Many persons need to be assured that the use of the respirator is only temporary until recovery of the normal respiratory mechanism. After an individual has been placed in the machine and the motor started, it is often helpful for the physician to breathe synchronously with the respirator and the patient until the latter learns to relax sufficiently to allow the apparatus to take over completely. If sufficient strength of the respiratory muscles is still present, breathing is often not synchronized and great fatigue may result from "bucking" the respirator. This can be avoided by proper instruction of the patient by the physician. The remainder of the care of cases of respiratory muscle paralysis is essentially the same as that of other spinal types of poliomyelitis. If there is "spasm" of the chest muscles and diaphragm, hot packs may be applied to the thorax through the portholes in the machine. Practically every manipulation required in the treatment of the patient can be carried out in the respirator by those experienced in the care of this form of infantile paralysis.

The great comfort produced in patients with respiratory difficulty when they are placed in the mechanical respirator and the fear that they may not be able to breathe when taken out of it leads to the early formation of a strong attachment to the machine. As a result, many persons are frequently unwilling to be taken out of it for even short periods of time. "Weaning" from the respirator should be started early. This is accomplished by taking the patient out of the machine six to eighteen hours after first placing him in it. The period without artificial respiration is determined by the clinical condition. Patients should never be allowed to become cyanotic before artificial respiration is started again. At first, individuals usually can tolerate only 15 to 20 seconds outside the respirator every three to four hours. The length of time spent out of the apparatus should gradually be increased and the intervals between each removal from it decreased. Using this method, it is not uncommon to see cases which had total respiratory muscle paralysis be free of the need for mechanical aid to breathing two to four weeks after the start of the disease. Early "weaning" may be responsible for the fact that not a single "respiratory cripple" has been seen in our hospital in the last three years although at least fifteen cases requiring the use of the respirator have been treated. In persons in whom only mild paresis of the respiratory muscles

is present a period of three to four hours in the respirator often produces sufficient relief of muscular fatigue so that no mechanical help is again needed for several hours in many of these instances adequate recovery of muscle function is present in a few days and artificial respiration is no longer necessary

Although Sister Kenny has condemned severely the respirator and has expressed the opinion that the application of hot packs to the chest wall is the treatment of choice in relieving respiratory muscle paralysis, there is no doubt in the minds of many experienced clinicians that the mechanical respirator is one of the most valuable pieces of apparatus employed in the treatment of poliomyelitis. The intelligent and early use of the respirator has saved the lives of many people. It must be emphasized however that this machine is of value only in the treatment of the respiratory embarrassment which results when paralysis of the muscles of respiration occurs and is not only not useful, but actually dangerous when used in cases of respiratory paralysis due to the medullary center disease or obstruction of the air way which occurs in bulbar poliomyelitis

Bowel disturbances—constipation and meteorism—are common in the spinal type of paralytic poliomyelitis early in the disease and should be treated by the administration of saline enemas. In individuals whose movement in bed is markedly limited by pain or paralysis constant attention should be paid to the care of the skin. Alcohol rubs and powdering at least twice a day are helpful in preventing bed sores. When bladder paralysis is present constant catheter drainage must be resorted to. For the first few days a Foley catheter may be used; this should be clamped off and allowed to drain only every four to six hours in order to maintain bladder tone. In cases in which inability to void is persistent for two or three days tidal drainage using 1:20,000 potassium permanganate as the irrigating fluid is instituted and maintained until bladder function returns.

No dietary restrictions need be imposed on patients except the avoidance of foods which leave bulky residues. The food should be prepared in a manner pleasing to the eye and palate. Fluids may be given in any quantity desired in young children and in those who refuse to take adequate amounts of fluid. Saline-glucose solutions may be given parenterally. Drugs for relief of pain must be given with great care. In patients with paralytic poliomyelitis, particularly in those in whom lower cervical cord disease is present since these may progress to bulbar and respiratory center involvement. Morphine and the barbiturates are never used in our hospital because of their depressing effect on the respiratory center. Acetylsalicylic acid (0.6 gm.) or acet-

(0.6 gm) combined with codeine (0.06 gm) are useful for relieving discomfort. Demerol (0.1 gm) given intramuscularly is highly effective in cases with severe pain. The use of sulfonamides, either for the prophylaxis of bladder infections or the treatment of other secondary bacterial complications, is contraindicated because of the observation of Toomey that the administration of any of this group of drugs may make the clinical course of poliomyelitis more severe. Careful bacteriologic study of any complications should be carried out and penicillin or streptomycin used depending on the type of bacteria involved. There is no evidence that the administration of convalescent serum has any beneficial effect on the course of paralytic poliomyelitis.

The chronic phase of poliomyelitis is best treated by the orthopedic surgeon trained in the therapy of this type of case. At least one or two years should be allowed to elapse after the acute onset of the disease before orthopedic measures such as fixation of joints or shortening of tendons are resorted to, in order to allow natural reparative processes to produce their full effects. The results which have been achieved by orthopedists in the rehabilitation of patients suffering the residua of the spinal type of infantile paralysis are truly remarkable. It is most important that every paralyzed patient be placed in the care of an orthopedic surgeon in the convalescent phase of the disease; he should decide when nonoperative procedures have produced their maximal effect and surgical treatment is necessary.

**Bulbar Poliomyelitis**—The type of treatment used in bulbar poliomyelitis depends, to a great extent, on the part of the brain stem involved, the subsequent clinical course and whether or not there is accompanying disease in the spinal cord. When the spinal type is present together with midbrain involvement, therapy for the former is that which has been described above. The various pareses and paralysis that occur with upper cranial nuclear dysfunction usually require no specific treatment; sewing together the eyelids or constant instillation of sterile oil into the conjunctival sac is helpful in preventing corneal ulcerations when an eye cannot be closed and physiotherapy to the face is of aid in dysfunction of the seventh nerve. Residual paralysis is rare when the upper cranial nerve nuclei are involved and total recovery of function, after varying periods of time, is the rule.

When the nuclei of the lower cranial nerves, particularly that of the tenth, are involved, therapy should be instituted early and carried out vigorously. The pharyngeal and soft palatal paralyses which are present place the patients in great danger of their lives because of obstruction of the airway due to pooling of secretions in the pharynx.

Anoxia may be of marked degree and these individuals require immediate treatment on admission to the hospital. Several methods of dealing with the problem of interference with breathing due to the inability to swallow are available. The patient may be placed flat on his back in a bed the foot of which is elevated about 2 feet off the floor and the pharyngeal collection of fluid drained off by gravity, the patient's head is turned to one side to facilitate the flow of saliva and mucus. A suction machine is often helpful in producing relief more rapidly. The prone position in bed with the head suspended in a sling outside the bed allows good drainage of fluids by gravity and prevents any interference with respiration as may occur in the supine position with the foot of the bed elevated due to pressure of the abdominal viscera on the diaphragm. Most patients with paralysis of the swallowing mechanism require oxygen. Since maintenance of an unobstructed airway is of first importance in the care of these cases, early elective tracheotomy has been recommended in selected instances by Galloway,<sup>8</sup> Glaser,<sup>9</sup> and Nelson Jones and Williams.<sup>10</sup> If this operation is to be performed it should not be delayed until an individual is in extremis. Undue delay may cause severe hypoxia and increase the danger of pulmonary edema. The criteria used by the Minnesota Poliomyelitis Commission<sup>11</sup> for carrying out an elective tracheotomy are: Recent onset of bulbar symptoms with evidence of progression of the illness during the period of observation; general appearance of toxicity especially with high temperature, rapid pulse, progressive difficulties in swallowing or the accumulation of secretions in the throat; and mental changes especially anxiety, apprehension, hyperactivity, confusion or euphoria in a patient with difficulty in swallowing. In our own clinic we have never found it necessary to resort to tracheotomy to save the life of a patient with bulbar poliomyelitis in spite of the fact that a fairly large number of cases of this type of the disease have been treated. Drainage of pooled secretions by gravity and mechanical suction has thus far been adequate in all of our patients. A more extensive comparison of the effectiveness of tracheotomy in contrast to the other methods of maintaining an unobstructed airway is necessary before the operation can be recommended as a routine procedure in selected cases.

In addition to obstruction of the airway, involvement of the lower cranial nerve nuclei presents a problem in the maintenance of good hydration and nutrition. In the early stages of the disease when swallowing is impossible, nothing must be given by mouth. Hydration is carried out by the intravenous or subcutaneous route. Great care must be exercised in avoiding the administration of excessive amounts of



sodium chloride or water in order to prevent pulmonary congestion. In young children proctoclysis may be useful. Gavage may be attempted after four or five days. The stomach tube should be passed with great gentleness and care and every effort made to avoid excessive stimulation of secretions since this may lead to an increase in obstruction of the airway, in a few patients gavage is impossible for this reason. The tube is allowed to remain in the stomach for ten to twelve hours per day and then is removed in order to minimize the danger of aspiration, gavage is repeated daily until the patient is able to swallow fluids without choking, when oral feeding is reinstituted. Formulas of various constitution containing an adequate amount of protein, carbohydrate, fat, vitamins and minerals are fed through the tube at periodic intervals or by slow constant drip in quantities sufficient to meet the daily fluid, caloric and vitamin requirements.

Involvement of the respiratory center in the medulla produces a characteristic picture of hiccoughing, followed by rapid, shallow, irregular respiration. In the cases where the brain stem alone is affected there is no weakness of the muscles of respiration. Individuals with this type of disease should be given oxygen continuously, positive pressure is helpful in many instances. The state of oxygenation of the blood is estimated frequently with the Milliken oximeter. These patients must never be placed in a mechanical respirator because it is impossible for them to synchronize their breathing with the machine due to the normal strength of the respiratory muscles and the irregular stimuli which come from the diseased respiratory center. Treatment in the respirator thus produces a great deal of fatigue and, in our experience, most individuals with respiratory center involvement do very poorly when given artificial respiration.

There is no treatment for the symptoms and signs which appear when the medullary circulatory regulating center is affected. Oxygen should be administered constantly and the state of oxygenation of the blood determined frequently. The prognosis is very poor in spite of all the supportive therapy such as caffeine, epinephrine or ephedrine, which is given.

Patients with bulbar poliomyelitis, particularly those with involvement of the lower cranial nerve nuclei or the medullary centers, require the constant attention of experienced clinicians and nurses. They must be watched carefully every moment of the early acute phase of the disease for signs of obstruction to the airway, anoxia and the like, and treated immediately when such manifestations appear. The outlook in respiratory and/or circulatory involvement is poor. The prognosis, when the swallowing mechanism is impaired, is dependent on



**Prevention of Poliomyelitis**—There are, at the moment, no means for preventing poliomyelitis Wesselhoef<sup>27</sup> and others<sup>5 20</sup> have pointed out that the administration of convalescent serum in the early phase of the paralytic form or in abortive or nonparalytic cases has no effect on the course of the infection Bahlke and Perkins<sup>29</sup> have shown that gamma globulin prepared from pools of normal plasma has no prophylactic effect Active immunization with virus vaccines is, as yet, without clinical value

### SUMMARY OF THE TREATMENT OF POLIOMYELITIS

The purpose of treatment in poliomyelitis is first to save life, and after that to relieve discomfort, to correct the effects of muscular dysfunction and to prevent and treat the emotional disturbances which may occur Good nursing care is of the greatest importance in the therapy of any type of infantile paralysis The primary purpose of treatment in cases with paralysis is the maintenance of as good function in the unaffected parts of the muscle as is possible in order that these may hypertrophy and take over the work of the fibers which have atrophied because their controlling neurones have been destroyed Thus, early and intelligent physiotherapy, ambulation as early as possible, and orthopedic treatment are of extreme importance The application of heat in one form or another is of proved value in relieving pain and discomfort resulting from muscle "spasm", it must be noted, however, that there is no specific effect of heat on the primary pathology of the disease, hot packs have never *cured* a case of poliomyelitis When the brain stem, pons or medulla is affected, special problems in treatment arise In certain cases the first and most important task is to save the life of the patient Maintenance of an unobstructed airway, administration of oxygen, suction of pooled fluids in the hypopharynx, and adequate hydration and nutrition are of greatest importance in this type of disease When the medullary respiratory and circulatory centers are involved, little save the administration of oxygen is of any value The treatment of abortive and nonparalytic poliomyelitis consists essentially of bed rest and relief of any discomfort that may be present

The cause of respiratory difficulty must be determined before treatment for it is undertaken When paralysis of the muscles of the chest and diaphragm are present the use of the mechanical respirator is often life-saving, in paralysis of the respiration due to respiratory center involvement or pooling of fluid in the pharynx with obstruction of the airway the mechanical respirator is absolutely contraindicated unless there is accompanying loss of function of the muscles of respiration



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### SYNDROME OF PROTRUDED INTERVERTEBRAL DISK

ERIC OLDBERG, M D \*

Although the condition to be described in this clinic may properly be called surgical it is so common that almost all general practitioners have experience with it, so that there is nothing out of place in including it in a medical clinic. The recognition of the syndrome of protruded intervertebral disk has so changed our thinking and so clarified the reasons behind chronic lumbago and chronic sciatica that everyone should make himself familiar with it. Before I show you cases I should like to give you the anatomical background of the condition and describe to you its symptoms and diagnosis

#### ANATOMICAL BACKGROUND

The intervertebral disk is a cartilaginous plate of varying thickness depending upon the portion of the spine in which it is located and which acts as a cushion and joint between the bony bodies of the vertebrae thus giving the spine a certain amount of elasticity. The disk itself is very fibrous, and is encircled by circumferential fibrous material called the *annulus fibrosus*. In the center of these encircling and strengthening fibers there is a soft matrix which is extremely springy, and is said to be enclosed in the substance of the disk under some tension. This is the *nucleus pulposus*, and I would say that on palpation in vivo or upon being removed it feels very much like a piece of live rubber, it is so resilient. It is almost pure white and is quite avascular. One might compare it to the soft rubber center of a golf ball.

The disk with its *nucleus pulposus* is attached to the bodies of the contiguous vertebrae above and below by extension of the *annulus fibrosus* onto the periosteum of the vertebral bodies and the cartilaginous plates which bound them above and below. In addition there are ligamentous structures which run in the axis of the spinal column up and down its entire length the most important of which are the anterior and posterior longitudinal ligaments. Since we are

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interested in posterior dislocations of the disk and ruptures of its material, we are, of course, chiefly interested in the posterior longitudinal ligament. This structure is thickest and most protective in the midline on the anterior surface of the spinal canal, and thins out somewhat as one proceeds laterally in this canal towards the foraminae through which the spinal nerves make their exits. This latter is one of the chief reasons, therefore, that the great majority of disk herniations occur laterally, where the longitudinal ligament is thin, rather than in the midline, where it is quite thick and well developed.

Theoretically, protruded intervertebral disk may occur at any point along the spinal column. Actually, however, perhaps 95 per cent of these lesions occur at the lower end of the lumbar spine—either at the lumbosacral junction or at the interspace between the fourth and fifth lumbar vertebrae. It has been estimated that about 60 per cent of all protrusions lie between the fifth lumbar and the first sacral vertebrae, 35 per cent or more lie between the fourth and fifth lumbar vertebrae, and the remaining 5 per cent or so are confined to the cervical spine. Ruptured disks with posterior protrusions are comparatively rare in the thoracic spine.

The usual type of injury which produces such a herniation is one which puts a sudden extra weight or strain upon the spinal column and at the same time twists it. Most of the patients I have seen have sustained their injuries by falling in a sitting position, by suddenly having an unexpectedly heavy weight put upon them, such as in stumbling and falling while carrying 150 or more pounds, or by having a fellow workman do the same thing while the victim is carrying one end of a heavy weight, or by having attempted to toss heavy sacks or lift heavy weights from one position to another while in a cramped or stooping position. When injuries of this sort occur, and there is a definite history of such injury in a fair percentage of cases, the annulus fibrosus is ruptured and some nucleus pulposus material herniates out into the spinal canal, usually laterally and usually against a caudal spinal root in the lower end of the lumbar canal.

### SYMPTOMS

The symptoms produced by such a rupture will usually begin with pain in the lower back and often somewhat off to one side of the midline. They may be comparable to what some years ago was so frequently diagnosed as sacroiliac strain. The patient may be able to work the remainder of the day or part of the day on which this incident occurs, but in my experience it is a very common thing for the patient to report that when he attempted to get out of bed on the following morn-

ing, the pain was so excruciating he was unable to do so. As a rule this pain remains localized in the back for a short period of time perhaps a few days or weeks, and then sciatic radiation begins although the latter may even appear at the time of the injury. The radiation may be only as far as the middle third of the posterior aspect of the thigh or more commonly, it may extend all the way down to the lateral side of the heel or ankle. Needless to say the symptoms thus described are those of the commonest form of disk protrusion although it should be recognized that if the protrusion or herniation occurs a vertebra or two higher in the lumbar spine radiation may be down the anterior aspect of the thigh and affect the knee jerk rather than the ankle jerk. At any rate it is when this back pain with its radiation down the leg has existed for a reasonable period of time or perhaps has disappeared and then spontaneously reappeared a few months later or has been exacerbated by reinjury that the patient finally comes to the doctor for other than physiotherapy or a hopeful palliative form of treatment.

The appearance and story of such a case is very typical. The patient states that he is uncomfortable day and night but that his chief discomfort is upon arising in the morning particularly if he has been sleeping on a soft and sagging mattress and for this reason numerous patients give a story of having sought comfort at night by sleeping on the floor. Bitter complaint is made of pain on bending forward even to tie the shoes. The patient may state that he has prickly or 'going to sleep' feelings down the affected leg usually down the posterior and lateral surfaces. Complaints of discomfort or disability affecting the other leg are quite rare, in my experience as are complaints of loss of urinary control although both of these things may occur and are serious—usually meaning that the protrusion of the disk is midline rather than lateral. The ordinary patient often will complain that coughing, sneezing or straining is excessively painful to the point of the patient not daring to do so and lastly the patient believes there is weakness in the affected leg chiefly manifested by discomfort and weakness in ascending stairs.

Examination of a typical case will show a patient who may look somewhat anxious from lack of rest and from discomfort. In walking he may limp slightly and seem to favor the affected leg. The angle of the spine is frequently carried at a tilt the tilt usually being away from the affected leg this being nature's method of endeavoring to widen the gap at the site of the herniation and thereby perhaps allow some of the extruded material to sink back into place. The normal lordosis will usually be lost and the lumbar muscles are in spasm as a rule and deep palpation over them in the li



area of the affected side will often be quite painful. The straight leg raising sign will be painful and positive within quite a restricted excursion on the affected side, as a rule, and fairly good with a much larger excursion on the normal or unaffected side. Atrophy of the lower leg does not usually appear except in rather late or protracted cases, but it should always be examined for, and measurements taken if any question exists. On testing for reflexes, by far the most common change is to find that while the knee jerks are equal and within normal limits, the ankle jerk on the affected side is either diminished or absent. On testing for sensation, it is common to find some diminution in pin prick and light touch sensation down the lateral aspect of the lower leg and lateral aspect of the foot—the first sacral root being most frequently affected.

### LABORATORY TESTS

As far as laboratory tests are concerned, they may chiefly be divided into three categories: x-ray, lumbar puncture, and injection of radio opaque substances. It is at this point that the schism has developed between those who feel it is cheaper, quicker and easier to make a clinical diagnosis and explore with these patients, than it is to be overthorough and still possibly be mistaken before operating. This is a matter which I shall, therefore, attempt to amplify at this point.

**X-rays**—X-rays should, of course, be taken. At least 75 per cent of the time they will not reveal any abnormality of significance, but this is true, needless to say, of any other part of the body in most pathological conditions. In old cases, however, or in severe ruptures with extrusion of much material, the commonest finding is to find a narrowing of the intervertebral space—most common between the fifth lumbar and first sacral vertebrae, or between the fourth and fifth lumbar vertebrae, since 95 per cent of ruptures occur here. It should be borne in mind, however, that the amount of extruded material in the average case is but a comparatively small percentage of the total volume of the disk, and since it is the extrusion, and, therefore, the loss of such material which would account for the narrowing of the interspace, we should not expect to see much narrowing in a large number of cases.

**Lumbar Puncture**—The next diagnostic procedure is lumbar puncture. In about 50 per cent of disk patients the total protein in the spinal fluid will be moderately increased, let us say up to 60 or 70 mg., rather than the normal of 30 or 40 mg. This does not always occur, however, and I would not be one to insist upon lumbar puncture in every case. If, however, there is any question whatever, or if there is

any possibility of any other lesion, such as tumor of the cauda equina lumbar puncture should naturally be performed and the fluid tested for all of its components the most important of which is total protein

**Injection of Radiopaque Substances**—As far as injection of radio-positive substance is concerned that is a question which has a good many ramifications. The methods used for myelography at the present time are chiefly two in number—either myelography with air or myelography with heavy radiopaque substances. If the latter is used it should be removed once the visualization and plate taking is completed

I may enumerate several of the advantages and objections to these procedures. As far as advantages are concerned if one has expert radiologic technique and interpretation they are at least theoretically of inestimable value both in making the diagnosis of the presence of the lesion and in diagnosing its location. There are a number of disadvantages however. In the first place, none of these techniques is foolproof, and none is infallible. We have all seen cases in which a filling defect seemed to be demonstrated and the exploration was negative, and we have seen other apparently normal myelographies in which exploration discovered a large herniation. Secondly, they put the patient to considerable expense both for time in the hospital and for cost of radiologic study whereas direct surgical exploration when a proper history has been taken and examination made will yield nearly as high a percentage of positive results with considerably less time expense and discomfort. Lastly there is always a question especially when dealing with a diagnostic procedure from which the patient may later attribute discomforts and disabilities and there is the additional danger of leaving a permanent radiopaque substance in the canal which may be demonstrated radiologically afterwards for many years. With respect to the latter it may also be stated that any neurosurgeon who has operated upon a cauda equina in which several cc. of lipiodol have been left for months or years can describe to you the solidified buttery appearance which this substance takes upon itself and in which the caudal roots become embedded and from which they are no doubt chronically irritated.

In summary therefore I would say that of the three laboratory diagnostic procedures above enumerated one should first always have x-ray plates of the lumbar and sacral spine second that one should always perform a lumbar puncture and have a laboratory examination of the fluid in any case in which there is any ambiguity whatever and third that myelography should be reserved for particular cases in which it seems especially indicated with the reservation that as our

radiologic technics improve and the substances used for myelography are also improved, this statement may eventually be altered to admit that myelography is an essential procedure, or nearly so

### ILLUSTRATIVE CASE HISTORIES

I shall now show you three cases illustrating different phases of the problem, and then discuss treatment

CASE I—This patient is a laborer, 31 years of age, who is employed by a freight express company. Three weeks ago he was loading boxes which weighed about 100 pounds apiece into a freight car. He was working in a stooped and cramped position, when in the midst of lifting one of the boxes, he felt a sudden "crack" in the back. He first sank to his knees and then crawled out of the box car and rested for a few minutes. When he attempted to stand up, he found that he could not straighten up and he accordingly reported to his foreman, who told him to go home and rest, which the patient did. On the following morning, when he awakened and attempted to get out of bed, he found himself unable to do so and the pain by this time had begun to radiate down the left leg as far as the outer aspect of the heel. This pain was continuous, but when he coughed, it was exacerbated, with radiation of pain beginning in the back and extending as far as the calf on the left side. The patient remained in bed three days and was somewhat improved so that he was then able to visit the company doctor who prescribed heat treatments, which the patient continued to have daily, though his trip to the doctor's office for this was about as much activity per twenty four hours as he could stand. A few days after the beginning of the pain, the patient also stated that he began to have numb, prickly feelings over the dorsum of the foot and lateral aspect of the ankle.

On examination, it is seen that this young man walks with a marked limp, favoring his left leg. His back is carried bent forward and tilted somewhat to the right, and one can palpate considerable muscle spasm in the lumbosacral area with some tenderness at the lumbosacral junction just to the left of the midline. The normal lumbar lordosis is gone. In examination of the lower extremities there is no atrophy on measurement, but the patient finds that his left foot is weak when he attempts to stand on tiptoe on that side, and he has also had some difficulty on climbing stairs in supporting his weight on his left foot as he attempts to plantar flex it. The knee jerks are equal and within normal limits, but the left ankle jerk is somewhat diminished as compared to the right. On testing for sensation, the patient states that there is slight numbness to pin prick and light touch on the lateral aspect of the dorsum of the foot. When the patient lies on the examining table and his right leg is raised, it begins to give him discomfort, as one approaches an angle of 90 degrees and thereby twists his back somewhat. The left begins to give pain almost immediately, and the patient cries out that he does not wish further extension of it when one exceeds a 30 degree angle.

**CASE II**—This patient is a 44 year old carpenter. He came into the hospital because six weeks ago a ladder was pushed out of place and he was precipitated from the second step of it onto the ground in a sitting position a distance of about two feet. This produced severe pain in the back which increased during the afternoon and caused the patient to go home early. On the following morning he found that he could not get out of bed and that he had pain radiating down the posterolateral surface of the left thigh and leg and some numbness of the great toe on the left foot.

Further history indicated that the patient had been having lumbago for some seven years and that some of his stages of this complaint had been associated with seric rheumatism. The patient is not sure as to how the lumbago began but he states that when playing sand lot soft ball he slid into a base and sprained his back. He is out of work for a month at this time and also had some seric. He is dull recovered from this but each year noticed pain in the same region in the back particularly during weather changes. Three years ago while he was with some friends the patient again got in acute back strain and this time was forced to stay out of work for two months. Again he had seric pain which gradually disappeared. Some time after this however the patient began to notice that his left calf was somewhat smaller in circumference than the right.

On examination the patient proves to be a well built and lightly obese man who walks with a cane. Examining his left leg and thigh, his trunk rather markedly forward. There is some spasm over the lumbar muscles and some pain on deep palpation in the lumbosacral area especially on the left side. The circumference of the right calf is 34 cm and that of the left calf is 31 cm. The knee jerks are equal and active but the left ankle jerk is absent. The patient states that at one time he "slapped" his foot in walking though this has disappeared now. Straight leg raising is markedly positive at an angle of 30 degrees on the left and at a 60 degree angle on the right. On testing for sensation the patient states that there is a distinct hypesthesia to pin prick and light touch over the lateral aspect of the left calf and over the extensor surface of the great toe. X-ray plates of the spine show some narrowing between the fourth and fifth lumbar vertebrae with a tendency of the spine to tilt toward the right. The patient is tired of his recurring disabilities and discomfort and wishes operative intervention.

**CASE III**—This patient is a 32 year old internal revenue agent employed by the Tax Collector's Office. He has already been operated upon so that I will describe the situation when I was first called in consultation. The patient had been moving from his home and a neighbor was helping him to lift an upright piano. In crossing a step the individual lost his hold and dropped his end of the piano suddenly putting more weight on the part that was being held up by the patient. The patient felt on the back a "snap" in the back and he collapsed to the ground and found that he could not get up. Both legs felt peculiar and numb and although someone was pouring warm water on them. After resting for a half hour the patient

to get to his feet with assistance, but his legs were very weak and he could hardly walk. There was pain in his back, but no particular radiation down the legs, on the contrary, they were numb. The patient remained home for two days, but found that he could not void his urine, and he was accordingly taken to the hospital.

At the time I saw him, he had been there about a week, during which time it had been necessary to catheterize him every eight hours and his legs had become weaker so that there was virtually no voluntary motion in them; there was a marked diminution in sensation to all modalities, becoming more pronounced as one tested distalward from the knees to the feet and toes. A low spinal puncture was done by me, which yielded slightly xanthochromic fluid with a total protein of 140 mg and a block on jugular compression.

In view of the advancing paraplegia and sphincter loss, I operated upon this man the next day and came down upon an enormous extrusion of nucleus pulposus material, in the midline between the fourth and fifth lumbar vertebrae. In order to remove it it was necessary to open the dura, enter the caudal sac, spread apart the caudal roots, incise the anterior dura and remove the extruded material through the dural incision. The piece removed was about the size of a terminal phalanx of an adult thumb.

Following this operation, the patient made a slow but steady recovery of function in his legs, though six weeks elapsed before he had any return of urinary sphincter control, and three months before this control was normal. At the time you see him now, three years after his operation, his chief objective residue is that his ankle jerks are both absent, and his chief subjective complaint is that he is still impotent.

### TREATMENT

We will now discuss treatment, which will, of course, be either conservative or radical. Any conscientious doctor would rather be conservative than radical, and I would state that I do not care to recommend operation until conservative measures have been adequately tried and until recurring symptoms with resultant disability have proved beyond doubt that one must take the bull by the horns and proceed surgically. This feeling would apply to the first case shown today.

As far as conservative therapy is concerned, there are really only two measures which may be taken, and they are about of equal importance. First the patient must abstain from all heavy lifting, especially in a stooping position. The mere fact that he has sustained a ruptured disk means that he from then on has a weak and injured back, and even with operative intervention, this should still be recognized and heavy strains avoided. The other important measure in conservative care is to see that the patient sleeps upon a stiffened mattress. Modern soft mattresses are an invention of the devil in this condition,

and the chief reason why most patients with protruded disk complain that they feel worse on arising in the morning. As brief contemplation will show a soft and sagging mattress allows the spine to buckle forward during sleep and thereby still further protrudes a protruding herniation with resultant increase in pressure on the caudal root which overlies it.

In my experience physiotherapy almost always does more harm than good. This is certainly true of mechanical manipulation either active or passive, and is even true of diathermy and similar treatments in a fair proportion of cases. In advising conservative therapy it is also important to consider other factors. These are chiefly the age and sex of the patient and the nature of his work. It is rare that we like to do a disk operation upon a patient of 70 years of age or over. Structures have begun to become so fixed and calcified by this time that we find that we cannot do as well surgically with our patients nor do they do as well clinically when surgery is attempted. Also it may be stated that at least in my experience a far higher percentage of female patients recover spontaneously than do male patients. And lastly it goes without saying that a patient who has a sedentary occupation can afford to experiment a longer time with conservative therapy than one who must be active. Therefore when we put all these features together—the age of the patient, the sex, the occupation, the severity and disabling effects of the pain, the chronicity and the tendency toward recurrence—we can begin to decide upon our course. Conservative measures must be exhausted and then operation considered. This is true of Case II in today's clinic.

Operations for protruded disks at the present time in this very young clinical entity, vary all the way from the minimal to the maximum. I imagine that a middle ground will eventually be found to be wisest. It is true that a certain number may be removed without any bone removal whatever. If they happen to lie just at the interspace and immediately beneath the ligamentum flavum on one side they may be exposed merely by removal of this structure and retraction of the caudal root with no bone removal whatsoever. At the other extreme we hear it advocated to operate upon these patients and not only to do the very major procedure of removing the entire disk in matter how small the protrusion but also to jam pieces of bone into the resulting traumatized space in an effort to solidify or stabilize the spinal column at that point. This to me has always sounded like a tremendously traumatizing performance and I believe I would prefer to let others prove its efficacy.

As far as my own feeling is concerned I believe that mistakes are

often made in surgery by lack of adequate exposure. For this reason, I see no special virtue in attempting to remove all disks with no bone removal from the contiguous laminae. I, therefore, remove as much as may be necessary to obtain adequate exposure, and this often involves a half or a third of one lamina, usually the fifth lumbar. On the other hand, once I have removed all loose pieces of disk material which I may extract and which I can feel in the cavity of the disk when I have removed the herniated portion, I desist and trust that nature will fix the remainder so that there will be no further protrusion. It is because of this, also, that I prefer the bone removal above described, since this will allow for a certain amount of decompression should future material be extruded at some future time from the interior of the disk. As far as the question of concomitant fusion is concerned, I believe it is still open. My practice has been to refer the case to the orthopedic surgeon in the first place, if the condition is predominantly in the back, with respect to symptoms. If, on the other hand, sciatica is the most prominent feature and back pain is secondary, I do the simple operation and let the fusion go. In such cases, it usually proves not necessary, and it can always be performed at some later date if required.

### PROGNOSIS

Final consideration in this paper should be the matter of prognosis and recurrence rate in these cases. In a syndrome really only fifteen years old as far as knowledge of its treatment is concerned, and less than that as far as a large number of cases under observation is concerned, no very definite statement can be made about prognosis and recurrence. Certainly we must recognize this fact, no matter what operative interventions we attempt, no matter how radical our surgery, and no matter whether we call in the services of an orthopedist for stabilization or fusion, once a patient has ruptured this important structure in the lower lumbar spine, apparently the most vulnerable and most abused portion of the back, he, from then on, has a weak back. I think it is utter foolishness to state that a patient who sustained his injury carrying 300 pound weights should return to the same work after operation.

As far as recurrence rates are concerned, it is literally too soon to make any very definite statements about them. I predict, however, that they will not be negligible. Once the annulus fibrosus is ruptured and nuclear material has herniated, there is certainly no law against further herniation at some future date, when, again, unusual strain is put upon this weakened structure. I, myself, have had a number of

symptomatic recurrences in mild degree and a few in sufficiently severe degree to justify reexploration the latter usually after a reinjury

During the next decade we shall have a much better chance to evaluate the varying technics of operative intervention above described We shall learn whether it is best to be conservative almost to the point of poor surgical exposure or to be radical almost to the point of brutalizing trauma We shall attempt to find out whether orthopedic stabilization of the spine should be an adjunct of neurosurgical removal of the herniated disk material In the meantime, since we do not know these things it is my strong philosophy that in our ignorance we should attack the obvious remove it and do as little else as possible.





## SUGGESTIONS REGARDING MANAGEMENT OF SEVERELY AFFECTED KIDNEYS

JOSEPH A. LAZARUS M.D.

A problem which frequently confronts urologists and internists is—how to treat a kidney which is severely infected or the site of other pathologic changes, and whose viability is uncertain. Following the general use of intravenous urography as a method of ascertaining renal function, pathologic renal changes are recognizable with increasing frequency. In many instances patients are told by their physicians that nephrectomy is indicated. When referred to urologists for surgery they are informed after thorough examinations that surgery can be deferred or completely avoided.

It is pertinent here to emphasize a few of the more common conditions coming within the aforementioned category which require careful evaluation before recommending radical therapeutic procedures.

### IMPACTED URETERAL CALCULUS IN THE NONINFECTED KIDNEY

An impacted ureteral calculus is one of the more frequent causes giving rise to impairment or retardation of diodrast excretion by a kidney. As most calculi are radiopaque they are readily discernible on the roentgen film. Inability to visualize a calculus may lead the examiner to eliminate this condition, but if he will remember that most uric acid calculi are radiotranslucent, he will insist upon a cystoscopic examination before ruling out calculus as the underlying cause of the failure of the kidney to excrete diodrast. Despite the fact that pain is a frequent symptom of ureteral calculus, innumerable examples of "silent stones" are seen.

The presence of leukocytes, with or without erythrocytes in the urine may signify infection in one or both kidneys, but the possibility must always be borne in mind that these cellular elements may be of bladder or urethral origin.

The passage of a ureteral catheter beyond a calculus followed by the intravenous administration of phenolsulfonphthalein or indigo carmine, often shows that the affected kidney is viable. Adequate catheter drainage of an involved kidney following the expulsion of a calculus, usually results in the prompt recovery of excretory function.

**IMPACTED URETERAL CALCULUS WITH PYONEPHROTIC KIDNEY**

The following history adequately illustrates the problem presented in this category

**CASE I**—Mrs A B, age 51 years, housewife and mother of five children, was first seen February 18, 1948, because of painless hematuria of one week's duration. She had experienced severe diurnal frequency, voiding every ten to fifteen minutes. There was no nocturia. There was slight burning on urination. A "functionless" left kidney was reported by the family physician following intravenous urography carried out on account of pyuria.

Roentgenograms showed a normal pyelogram of the right side. The left pelvis showed no dye up to two hours after administration. In the lower segment of the left ureter in close proximity to the bladder was a shadow approximately the size of a lemon pit, which on shadowgraphy proved to be a ureteral calculus.

Cystoscopy disclosed no abnormalities of the bladder, although there was thick, foul smelling, purulent urine. The right kidney was easily catheterized, the urinary specimen obtained was essentially normal, and the phenolsulfonphthalein returned in good concentration three minutes after intravenous administration. The left catheter encountered an impassable obstruction 1 cm from the bladder. *Escherichia coli* was recovered on culture from the bladder urine. Blood chemistry was within normal limits.

With this data, the question obviously arose as to whether there was a devitalized pyonephrotic kidney resulting from an old "silent" impacted ureteral calculus, or whether the failure of the kidney to take the diodrast was merely owing to temporary inhibition consequent upon back pressure caused by the calculus. The patient was told that the exact status of the kidney could be determined only after the calculus was removed and renal drainage effected. If this procedure failed to restore renal function, it would be necessary to remove the kidney at a later date.

Ureterolithotomy was accomplished February 25, 1948, and nine days later a ureteral catheter was easily passed to the renal pelvis and considerable turbid urine drained. Intravenous indigocarmine returned in good concentration from the left kidney in three minutes. The urine specimen from the kidney showed *Staphylococcus aureus* on culture.

Penicillin and sulfonamides were administered in liberal dosages, and the renal pelvis was lavaged at frequent intervals with NU-445\*. With this routine the kidney progressively improved. It is now manifest that complete recovery will follow.

*Comment*—The foregoing clearly illustrates the value of conservatism when dealing with a kidney apparently seriously infected and devitalized because of an impacted ureteral calculus. It also proves the

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\* See footnote page 1423

fallacy of placing sole reliance upon the intravenous pyelogram to ascertain the state of viability of a totally obstructed kidney. The best procedure with these patients is to defer a decision regarding the advisability of nephrectomy until the obstruction has been overcome or eliminated so that the effect of drainage in promoting improvement of renal function can be ascertained. This requires considerable time and the exercise of extreme patience—well worth while in attempting to conserve irreplaceable renal parenchyma.

### HYDONEPHROSIS ASSOCIATED WITH URETERAL STRICTURE

CASE II—Mr J. M., aged 56 developed chills, fever and right lumbar pain several months following destruction of a papillary carcinoma of bladder and implantation of radium emanation seeds. The tumor was situated in close proximity to the right ureteral orifice. Urine obtained from the bladder was thickly purulent. The right renal pelvis was cannulated with considerable difficulty because of stricture of ureteric orifice; urine obtained from the kidney was purulent. Phenolsulfonphthalein administered intravenously was returned in poor concentration from kidney in fourteen minutes. *Escherichia coli* and *Pseudomonas aeruginosa* were isolated on culture.

Three days later cystoscopy was again carried out because of persistent chills, fever and severe dysuria. Only with the greatest difficulty was it possible to pass a spiral catheter to the renal pelvis. Sluggish flow of thick purulent urine followed. Excretory pyelography disclosed a normal left pelvis, but the right pelvis failed to take the dye. A retrograde right pyelogram showed severe ectasia of the pelvis and ureter.

The patient was informed that the right kidney was severely involved and would probably require removal. But before recommending surgery I suggested that an attempt at conservative treatment might lead to improvement of renal function and possibly to kidney salvage. The patient readily agreed and ureteral drainage of the renal pelvis was carried out at intervals of four to five days. The pelvis was irrigated with MU-445. The patient was treated with repeated courses of sulfonamides (sulfadiazine and sulfamerazine in equal doses). After six months the obstruction at the ureteric orifice was completely relieved; the urine from the kidney showed an occasional leukocyte and was free of organisms. All urinary symptoms disappeared.

*Comment*—This report indicates what can occasionally be accomplished in apparently completely devitalized kidneys consequent upon strictures. Before instituting a course of treatment of this nature it is advisable to explain the problem involved to the patient and to the attending physician and the specific treatments required. They must also be told that if the kidney fails to respond to this course of treatment, nephrectomy becomes exigent.

**PYONEPHROSIS UNASSOCIATED WITH CALCULUS OR STRICTURE**

CASE III—Mr J S, aged 54, developed fever, pain in left flank, increased urinary frequency, dysuria and cloudy urine one month after prostatectomy for prostatic calculi

Cystoscopy was performed and 2 ounces of thick, purulent urine was obtained from the bladder. The renal pelvis were easily catheterized, and 15 cc of thick, purulent urine was obtained from the left. Phenolsulfonphthalein administered intravenously was returned in good concentration from the right kidney in three and one half minutes, but no dye was obtained from the left after ten minutes. Rectal temperature was 103.6° F. *Staphylococcus aureus* was obtained on culture of left kidney urine, the right kidney urine was sterile. Bilateral shadowgraphy failed to show a calculus in either kidney or ureter. A left retrograde pyelogram disclosed severe ectasia of the pelvis and calices.

Treatment consisted in biweekly lavage of the renal pelvis with NU-445, and sulfonamides by mouth. After eight weeks the urine from the left kidney showed scattered leukocytes, and the phenolsulfonphthalein return was good in four minutes.

*Comment*—In this patient the temptation to remove a severely infected kidney was great, especially in view of the presence of a normal kidney on the opposite side, and because of the uncertainty of results following conservative treatment. The attempt to save the kidney was made only after a thorough discussion with the patient regarding his condition, and the probability of a favorable result without resort to surgery. He then consented to undergo a prolonged course of pelvic lavage. The result exceeded our greatest expectation. The pyonephrosis was probably caused by an ascending infection from the bladder.

**RENAL-VISCERAL FISTULAS**

CASE IV—Mrs D M, a housewife aged 58, following removal of enormous benign adenomatous cyst from right lobe of liver developed a fistula between the lower calyx of the right kidney and the cavity in the right lobe of liver from which the tumor was removed.

Although the kidney was severely infected (the urine showed many pus cells microscopically, and *Aerobacter aerogenes* on culture), and despite the presence of a normally functioning left kidney, conservative treatment was advised and found acceptable by the patient. This included repeated dilatation of the right ureter and lavage of the pelvis with NU-445, and the administration of properly selected sulfonamides and mandelic acid. The result was complete obliteration of the fistula and eradication of infection from the kidney.

*Comment.*—The vast majority of renal visceral fistulas heal under proper conservative treatment. Unless this is borne in mind many kidneys will be sacrificed that would otherwise be responsive to treatment.

#### PYONEPHROSIS IN UNILATERAL ACQUIRED KIDNEY

CASE V.—Mrs. M. B. R., aged 82 underwent nephrectomy for left renal cavernous tuberculosis seventeen years ago. About one year later she developed signs of tuberculosis in right kidney later complicated by perinephric abscess. Evacuation of abscess resulted in complete abatement of symptoms lasting two years. At this time (December 1935) it became necessary to operate upon the right kidney for pyonephrosis and pyoureter. The operation disclosed a large, tense pyonephrotic kidney with an abscess in the wall of the ureter directly below ureteropelvic junction. Nephrostomy and drainage of renal fossa were done and after a stormy convalescence the patient left the hospital in three months.

During the next thirteen years she was under my constant observation and treatment which consisted of frequent changes of the nephrostomy tube, tuberculin injections and later the administration of sulfonamides, penicillin and streptomycin. Contrary to my advice the patient insisted upon being married in 1937 she became pregnant and was obliged to undergo a therapeutic abortion. In 1943 a successful cholecystectomy was accomplished for recurrent attacks of biliary colic due to cholelithiasis. She finally succumbed December 31, 1947 from diffuse miliary tuberculosis and liver abscess.

*Comment.*—This patient illustrates that with proper care a fairly comfortable existence can be maintained for many years, despite the presence of only a small amount of functioning renal tissue. The importance of adequate and free renal drainage in my opinion has been the factor most responsible for the long survival of this patient.

#### BILATERAL CALCULUS INFECTED HYDRONEPHROSIS

CASE VI.—Miss E. S., aged 67 was first seen February 13, 1941 at which time she complained of left lumbar pain, hematuria and pyuria of ten days duration.

Genitourinary examination disclosed bilateral renal calculi, hydronephrosis and impacted left ureteral calculus. The patient did not show symptoms of hyperparathyroidism.

A left nephrolithotomy and ureterolithotomy were done on February 20, 1941. The renal pelvis was found enormously dilated, about the size of a Rugby football with the cortex strikingly attenuated. Very little renal parenchyma could be visualized or palpated.

On March 5, 1941 right pyelonephrolithotomy was carried out. This kidney was also found to be greatly enlarged and hydronephrotic; the calices were greatly dilated.

Following discharge from the hospital with two nephrostomy tubes in situ, the patient returned to the office for routine bilateral pelvic lavage. Intravenous pyelograms (July, 1941) showed extremely dilated calices on the right side, the left kidney did not take the dye. A group of shadows (calculi) were seen in the lower pole of the right kidney.

Nephrostomy tubes were removed six months after operation.

The patient returned November 13, 1943, after an absence of two years, complaining of right lumbar pain and frequency. At this time there was a group of shadows in the lower pole of the right kidney, and several small shadows in the region of the middle calyx. The left kidney was free of shadows, but there was a small shadow in contact with the left catheter opposite the spine of the ischium.

Bilateral pelvic lavages were carried out at weekly intervals until May, 1944, when the patient complained of severe pain in the right lumbar region. The roentgen film showed a large coral calculus in the pelvis of the right kidney and two small calculi in the region of the lower pole. The left kidney appeared to be free of shadows.

A right nephrolithotomy was done on May 17, 1944. The patient was discharged with a nephrostomy tube in situ.

Bilateral pelvic lavages were resumed at weekly intervals. On August 2, 1944, a roentgenogram again showed several shadows in the region of the right kidney. A film taken January 12, 1945 showed one large shadow in upper pole of right kidney and a few smaller shadows in lower pole. For the first time since operation, this film disclosed a few small shadows in lower pole of left kidney. A roentgen film made on December 18, 1945 revealed a shadow about the size of a large bean in the lower portion of left kidney. A roentgenogram on May 20, 1947 showed a large triangular shadow in the pelvis of the right kidney, and a smaller adjacent one. The left kidney presented two shadows in the pelvis and a group of smaller shadows in the region of the left wing of the sacrum.

July 9, 1947. Left nephrolithotomy and introduction of a large nephrostomy tube because of severe perinephritis and renal infection (infected hydronephrosis).

July 12, 1947. Operation on the right side disclosed a large pyonephrotic kidney containing many calculi. The calculi were removed and a nephrostomy tube was introduced. The patient was discharged from the hospital with bilateral nephrostomy tubes in situ.

Since July 12, 1947, treatment has consisted of high acid ash diet, frequent daily irrigations of renal pelvis through nephrostomy tubes with Solution G, weekly irrigations of pelvis through ureteral catheters, using NU-445, and alternating courses of sulfonamides, penicillin and mandelic acid, depending upon the nature of the bacteria obtained from urine on culture. Under this routine the patient continues to live with a fair degree of comfort.

*Comment*—This patient is within a category in which conservative therapy is not one of choice, but of necessity. Constant attention to

details by patient and physician is necessary to maintain (a) free drainage from the pelvis of the involved kidneys (b) eradication of infection in order to preserve so far as possible the greatly reduced mass of functioning renal parenchyma

### DISCUSSION

The modern trend in urology is toward extreme conservatism in the treatment of renal disease. With the advent of the latest chemotherapeutic means and antibiotics results in conserving renal tissue have greatly improved. Following the wide use of excretory urography by physicians, increasing numbers of patients with renal abnormalities are being referred to urologists much earlier than in the past. In order to further improve results in the conservation of renal parenchyma, a more comprehensive exchange of information between urologist and internist becomes necessary.

Probably one of the most important considerations is that the viability of a diseased kidney cannot be ascertained with any degree of certainty, especially in the presence of an obstruction. It is immaterial whether the obstruction is due to ureteral stricture or calculus with or without infection. Excretory urography in this category merely indicates that a kidney fails to take the dye and is probably damaged. Further considerations must be deferred until the obstruction is relieved and infection controlled.

The methods commonly used to relieve obstruction in this category largely depend upon (a) the presence of systemic manifestations such as chills, fever (sepsis) and pain (b) the character of the organism recovered on culture in examples of urosepsis and (c) the status of the uninvolved kidney.

It should be noted that the chances of obtaining favorable results probably depend to a great extent upon the promptitude of establishing drainage from the affected kidney. In patients with systemic manifestations resulting from urosepsis, the need for quick and complete relief of obstruction is urgent. In those with obstructing ureteral calculi prompt ureterolithotomy is the more efficacious procedure. Where the obstruction is due to stricture of the ureter or ureteropelvic junction which cannot be overcome with ureteral catheters even after complete anesthesia temporary palliative nephrostomy may be the procedure of choice. After this operation the stricture which is practically always accompanied by some degree of spasm usually subsides sufficiently to permit the subsequent passage of ureteral catheters and bougies.

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When obstruction is incomplete, and a ureteral catheter can be in

troduced into the renal pelvis, but where the patient presents systemic manifestations of urosepsis, the question arises as to whether a ureteral catheter, or even two ureteral catheters, will suffice to drain the affected kidney effectively and thus relieve distressing symptoms. This question can best be answered by introducing one large catheter or two smaller ones into the renal pelvis and noting whether or not there is adequate drainage. When the urine is too thick to pass through the eye of the catheter, a supplementary nephrostomy is indicated.

Any contemplated procedure in this group of patients is based upon the status of the uninvolved kidney. If the kidney, after suitable investigation, proves to be impaired, it may become necessary to abandon prolonged nonsurgical conservative measures and resort to more radical procedures, such as nephrostomy or pyelostomy.

While chemotherapy and the various antibiotics have proved effective in treating urinary infections, it is important to remember that no drug is effective in completely eradicating a severe renal infection in the presence of impairment of renal drainage. It might therefore be well to point out a few important principles involved in attempting to promote drainage in a badly diseased kidney.

Although the scope of this paper does not permit a detailed discussion regarding the technics utilized by urologists in draining obstructed kidneys, it is however necessary to know that for drainage to be effective, it must be thorough and prolonged. For example, in ureteral stricture the ureter must be dilated at frequent intervals, and the catheter left in situ for hours or days, depending upon the degree of infection. Where this fails to accomplish results, pyelotomy or nephrotomy should be carried out and the tube left in place sufficiently long to accomplish the desired result. This may require weeks or months. There should be no hesitancy in sending a patient home from the hospital with a nephrostomy tube, and insisting that he wear it until free drainage through the ureter can be restored.

The effectiveness of supplementary treatment of urinary infections with chemotherapeutic agents and antibiotics depends upon correct identification of the responsible organism. To treat an infected kidney effectively, the physician must consequently have the cooperation of a trained bacteriologist. The former practice of relying upon group identification of bacteria by stained smears is no longer acceptable. In order to obtain the maximum effect of treatment, frequently repeated cultures of properly taken specimens of urine are indispensable. When the organism is identified, it is incumbent upon the physician to choose the drug best suited for its rapid destruction.

In certain instances I have found it of inestimable value to carry

out assays upon the drug and organism in order to determine the possible effectiveness of treatment. This is particularly true when dealing with such organisms as *Pseudomonas aeruginosa* especially the mucoid variety, and *Streptococcus hemolyticus*.

Experience with the sulfonamides has convinced me that in many instances where one sulfonamide seems to be ineffective when given alone it will clear up an infection when given with another sulfonamide of similar chemical nature, such as sulfadiazine and sulfamerazine. In resistant infections with organisms of the gram negative group, simultaneous treatment with mandelic acid and streptomycin often proves effective.

During the past year we have been carrying on experimental work with a new sulfonamide, NU-445\* and after considerable study have used it with advantage in treating stubborn renal infections caused by *Pseudomonas aeruginosa* and *Escherichia coli* where sulfadiazine and/or streptomycin failed to eradicate the pathogens. The drug was administered orally in doses varying from 4 to 16 gm daily without untoward effects and without the need for concomitant alkali medication. It was also used in 20 per cent solution for pelvic lavage.

In dealing with impairment of both kidneys it is of the utmost importance to carry out measures aimed at conserving every bit of functioning tissue. In the case of multiple renal calculi as exemplified in Case VI bilateral nephrolithotomy may have to be performed and nephrostomy tubes left in situ either permanently or for long periods depending upon the degree of renal involvement. Chemical analysis of the calculi and the pH concentration of the urine indicate the kind of medication required to lavage the pelvis while the bacteriologic examination of the urine and the identity of the specific bacteria will suggest the nature of the drugs to be administered. High acid ash diet is of value in these patients. Repeated and systematic cystoscopic ureteral dilatation is necessary to keep the ureters patent. Before deciding on the advisability of removing nephrostomy tubes it is necessary to ascertain that the kidney is free of calculi and infection and the ureter completely patent. In many patients it is virtually impossible to prevent the reformation of calculi when it may become necessary to remove calculi at frequent intervals. The procedure is simple and can often be accomplished through the nephrostomy opening under sodium pentothal anesthesia. Suitable investigations must be made in this group to rule out parathyroid tumor (hyperparathyroidism).

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\*"A Clinical Study of a New Sulfonamide (NU-445) in the Treatment of Urinary Tract Infections" to be published in the *Journal of Urology*. NU-445 supplied by Dr. Leo A. Jark of Hoffman-LaRoche Inc., Nutley, N. J.

We have found that in many patients the stones are composed of triple phosphates and the urine is highly alkaline. Here we have used Solution G in irrigating the renal pelvis through the nephrostomy tubes as well as through the ureteral catheters. At times it becomes necessary to irrigate the pelvis frequently during the day, and a member of the patient's family is then instructed in the method of carrying out pelvic lavage at home through the nephrostomy tube. Unfavorable results are rare.

### CONCLUSIONS

Failure to visualize a renal pelvis in excretory pyelograms should not lead to the presumption that the kidney is devitalized, or so seriously involved as to require nephrectomy. The inability of a kidney to excrete dye may be due to temporary inhibition of function resulting from obstruction or infection, or both. Many kidneys can be salvaged if an attempt is made to reappraise their functional status following the establishment of free renal drainage and the control of infection. This is effected by ureteral catheter, pyelostomy or nephrostomy, depending upon the nature of the obstruction, the degree of urosepsis, and the status of the other kidney. The establishment of drainage by cystoscopic ureteral procedure, whenever possible, is preferable to nephrostomy or pyelostomy. Drainage, to be effective, must be carried out over long periods. It is therefore advisable to obtain the complete cooperation of the patient before instituting a course of treatment, by carefully explaining the problem involved and the exact nature of the contemplated treatment. He must be made to realize that, despite treatment, restitution of renal function may fail and nephrectomy become necessary.

Constant access to a reliable bacteriologic laboratory is indispensable in the achievement of maximum results. Unless the identity of the organism responsible for the infection is established, one cannot expect to derive full benefit from our modern chemotherapeutic agents and antibiotics which are so essential in correct treatment. Bacteriologic assays are of inestimable value in determining the selection of the most effective drugs to combat renal infections. To prevent the possibility of drug resistance, once a drug is chosen, it is necessary to use it in large doses and for a sufficient time to completely eradicate the responsible organism. The effectiveness of sulfonamides appears to be enhanced when used in combination, i.e., two sulfonamides of similar chemical structures, instead of one.

Ureteral dilatation and nephrostomy or pyelotomy are often indicated in the treatment of severely diseased kidneys. If infection is pre-

dominant especially with the gram negative organisms irrigations of the renal pelvis with NU-445 is highly recommended. In examples of calculosis or rapidly recurring massive phosphatic renal calculi in the presence of highly alkaline urine frequent irrigations of the pelvis through the nephrostomy tube and through the ureteral catheter with Solution G and the acid ash diet are highly desirable. Hyperparathyroidism must be ruled out in this group of patients.

In dealing with vital irreplaceable renal parenchyma every attempt to conserve tissue should be made, regardless of the efforts required on the part of the patient and physician to accomplish this end. Nephrectomy here should be considered a procedure of last resort.

NEW YORK CITY

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## VENTRICULAR PREMATURE CONTRACTIONS (EXTRASYSTOLES) A THERAPEUTIC CHALLENGE

ITALO F. VOLINI, M.D., F.A.C.P.\*

One often wonders whether therapeutic nihilism is born of an attitude of the futility and uselessness of therapy or the ignorance of the subject of therapeutics and its materials. Polypharmacy and many other unscientific measures have been justly swept away by the concentration of powerful scientific light upon the hodge-podge prescribing of the older days. Science demands the specific drug for the treatment of the disease. In the absence of the specific method treatment cannot be applied. The attitude of therapeutic nihilism results. There are, however, varying degrees and grades of specificity. A full knowledge of the potentialities as well as the limitations residing in several possible modes of treatment may often be of great benefit to the patient. Different drugs may possess therapeutic activity in the problem under consideration. Sodium salicylate for example can be substituted by eight equally effective salicylates if proper dosage and absorption equalization is arranged.

CASE I.—Mrs. C. P. depressingly introduced her story with the statement that she was told she had extrasystoles. "They have the same significance as a few gray hairs may have, so forget them." She tried this form of therapy but, as she states, "I can't because my heart jumps up in my throat it turns over, does frequent flipflops and, worst of all, acts up when I try to get to sleep." The result is hyperexcitability, nervousness, insomnia, nocturia and more disturbing, the conviction that serious heart disease is present no matter what the doctor told her. A housewife 50 years of age, para 4, her major complaint concentrates upon the "skipping" or "stopping" of the heart for the past five years. Belching of gas without special reference to the time or character of the foods has been present for fifteen years. There is some pain and stiffness in the back, shoulders, arms and fingers. She remembers no serious illnesses or operations. Her menstrual periods stopped fourteen years previously without much associated disturbance. She has known of some elevation in the blood pressure for ten years but the readings were not imparted to her.

The physical examination corroborated the patient's complaint in the evidence presented by the irregular pulse waves. This irregularity of the pal-

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pated pulse wave when performed with synchronous auscultation at the heart did not completely clarify the diagnosis of the arrhythmia because only occasionally could the compensatory pause be accurately detected. The blood pressure was 200/106. A slight periarterial streaking was noted in the eye-ground examination, however, tortuosity was absent. The heart showed slight enlargement to the left, measuring 10.5 cm to the left of the midsternal line. There were no murmurs. The sounds were strong. There was an evident arrhythmia, presumably frequent ventricular premature contractions, but

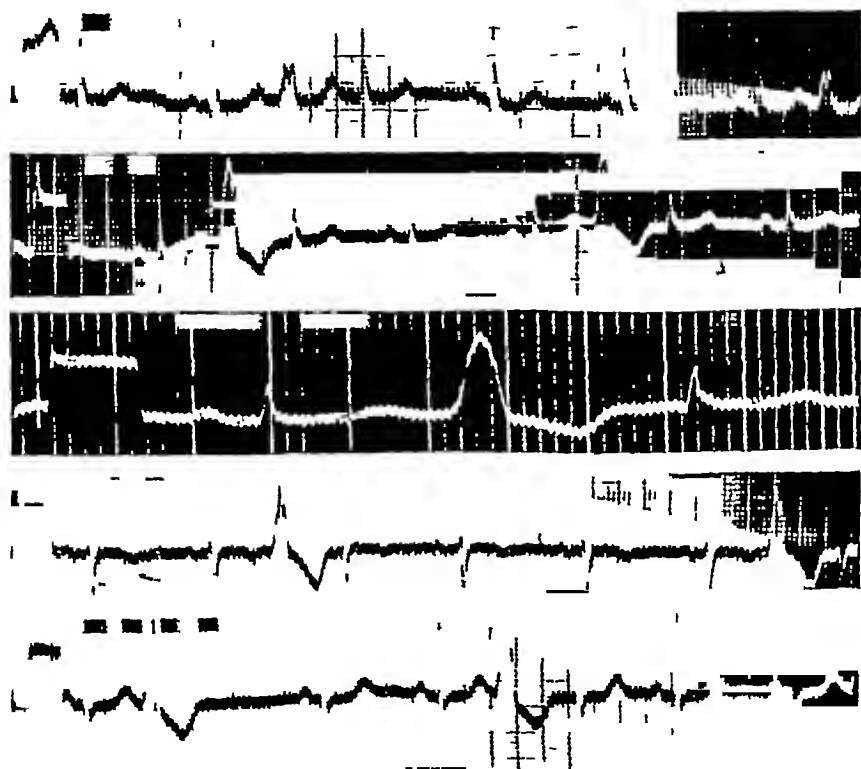


Fig 171—Mrs C P. Ventricular premature contractions originating in the right ventricle, near the base of the heart. These are not interpolated extrasystoles, as close measurement will disclose.

the diagnosis could not be definitely made by auscultation alone. The abdominal wall showed considerable relaxation with some diastasis, but tumors, masses, areas of tenderness and rigidity were not detected. The reflexes were normal. A definite prolapse of the uterus with protrusion of a lacerated scarred cervix was easily seen. The blood count, urine and Kahn were normal. The 2 meter chest film corroborated the slight left heart enlargement but in addition showed some moderate widening of the aortic shadow. When checked in the oblique positions by the aid of the fluoroscope the widening was apparent only in the anterior posterior views.

The electrocardiogram (Figs 171, 172) shows the heart rate of 80 with

frequent ventricular premature contractions (extrasystoles). They appear unifocal in etiology. They are of right ventricular origin arising in the base of the heart rather than the apex. The confusing clinical pattern is easily explained by the electrocardiographic tracing. There is no compensatory pause except in the one instance noticed in the beginning portion of the C. F. IV strip. Except for this one, each ventricular contraction is followed by a nodal premature contraction (extrasystole) with very slight aberration. Presumably the ventricular premature contractions arising near the base of

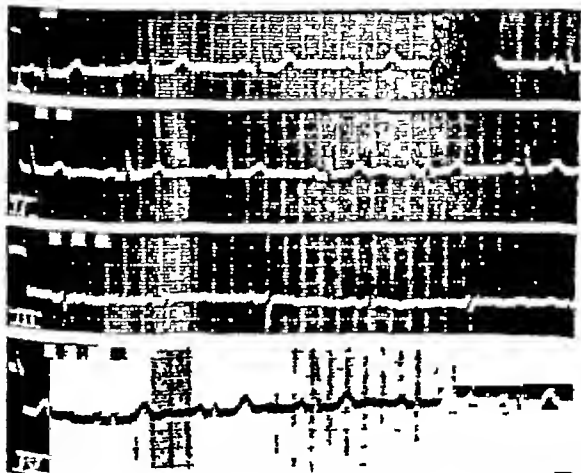


Fig. 17.—Mr. C. P. D. appearance of ventricular premature contractions following medication described in the text.

the heart produced some weight degree of moderate stimulation which irritated the sinoatrial node to activity producing nodal extrasystoles or these latter could arise independently. Due to some or possibly all of the above factors a mild nodal irregular premature a possible observation was produced on the basis of the long history of tachycardia and premature contractions.

**Treatment and Course.**—The decision was made to treat the arrhythmia, as well as to attempt to relieve the chronic pain. The extrasystoles were considered to arise from two nodal sources, one nervous or functional, the other reflex from the mild characteristic. Therapeutic experience has demonstrated that the reflex type of arrhythmia and is well tolerated under such circumstances. The patient was given the following combination of drugs:

R<sub>x</sub>

Phenobarbital	0 6
Quinidine Sulphate	90
Acetophenetidin	12 0
Salysal	16 0

Mix and divide into capsules No 60

Directions A capsule to be taken after meals and at bedtime.

The patient returned in two weeks stating the pains had disappeared but the heart still bothered her. This was particularly stressed by a dramatic pose in which she grasped her neck with both hands, the palms facing the ceiling of the room. The hyperirritability of the anxiety type indicated the necessity for sedation. She was told to take a teaspoonful of the following mixture in a little water after her meals and to double the dose at bedtime.

R<sub>x</sub>

Phenacetin	20 0
Potassium Bromide	20 0
Sodium Phenobarbital	1.5
Lixa Beta to make	240 0

Shake

Upon her return two weeks later she announced she was cured, that this was the first relief she had ever obtained. Fortunately the electrocardiogram substantiated her statement, demonstrating the absence of the ventricular premature contractions, although there still was present a P-R interval of 0.2 second, left axis deviation, slight slurring and a somatic tremor. The blood pressure was 158/90. She was told to continue the medication only in the evening, a teaspoonful in water at bedtime. There have been no recurrences, and evidences of bromism in the blood level or skin have not appeared.

*Comment*—The improvement or recovery is not attributed to the potassium ion. Experience with potassium medication either as chloride, citrate, or acetate has been very discouraging in the management of ventricular premature contractions. The sedative activity of the bromide and the phenobarbital components are given the credit for the improvement. This is frequently noted even where the extrasystoles do not disappear. The apprehensive factor is allayed by diminishing or abolishing somewhere in the reflex arc the consciousness of the disagreeable sensation of irregular heart action.

#### PHYSIOLOGICAL CONSIDERATIONS

Ventricular premature contractions are the most frequent arrhythmias encountered in the ambulatory patient. They may have their origin in any location in the heart. While specialized focalizations ordinarily initiate and control impulse production in the heart, the inherent potentiality of rhythmicity or automaticity (impulse forma-

tion) is a property possessed by all cardiac tissue. If heart muscle adjacent to a focus of abnormal stimulus production is not in the refractory phase it is irritable or stimulable. It responds with another property possessed by heart muscle, namely contractility. In addition to these three properties of heart muscle—rhythmicity, irritability and contractility, there exists conductivity. This is the ability to transmit impulses over the cardiac tissues. It is quite obvious then that premature contractions, particularly the ventricular types, are distinctly abnormal contractions. The stimulus arises in an abnormal site. Secondly it is transmitted over abnormal pathways, contiguity rather than the normal conducting system determining the route of transmission. The muscle contraction likewise spreads as the result of contiguity stimulation. Conduction and contraction extend from one ventricle to the other rather than the normal synchronous simultaneous distribution of stimulation, conduction and contraction to both ventricles. Necessarily time relationship in the cardiac cycle is usually disturbed.

Generally when they appear occasionally little or no disturbance results in the cardiodynamic effects. If however they are very frequent, particularly when associated with organic heart disease, some impairment in the cardiac minute volume output may be produced. However the etiologic heart disease and the condition of the heart muscle is the much more important determining factor.

#### CLASSIFICATION

The cause of the genesis of the focal impulse is unknown. Many individuals in fact the great majority with ventricular premature contractions do not possess heart disease, nor do they necessarily have any increased liability to develop heart disease. It has thus become convenient to classify clinically the ventricular premature contractions into the following four groups. This classification aids considerably in determining the course of the therapeutic procedure.

1. Nervous or functional in origin. Here there cannot be demonstrated any direct or associated cause despite a thorough careful history, physical examination and laboratory study. The response in this group to therapy is best obtained by the sedative group of drugs represented by the bromides, phenobarbital or chloral hydrate. Small dosage will frequently accomplish the desired effect.

2. Reflex origin. There is the frequent clinical picture of gastric ulcer, gallbladder and liver disease, have associated extrasystoles in the clinical picture. a) dietary, medicinal or operative b)

diseases will cause the extrasystoles to disappear. Likewise, functional gastrointestinal disorders, when treated, will show the disappearance of the arrhythmia.

3 Toxic etiology. One of the common causes of ventricular premature contractions is digitalis. This drug may produce a characteristic grouping of extrasystoles which is called *digitalis bigeminy* or *trigeminy* (Fig 173).

In the presence of extrasystoles of nervous or functional etiology,

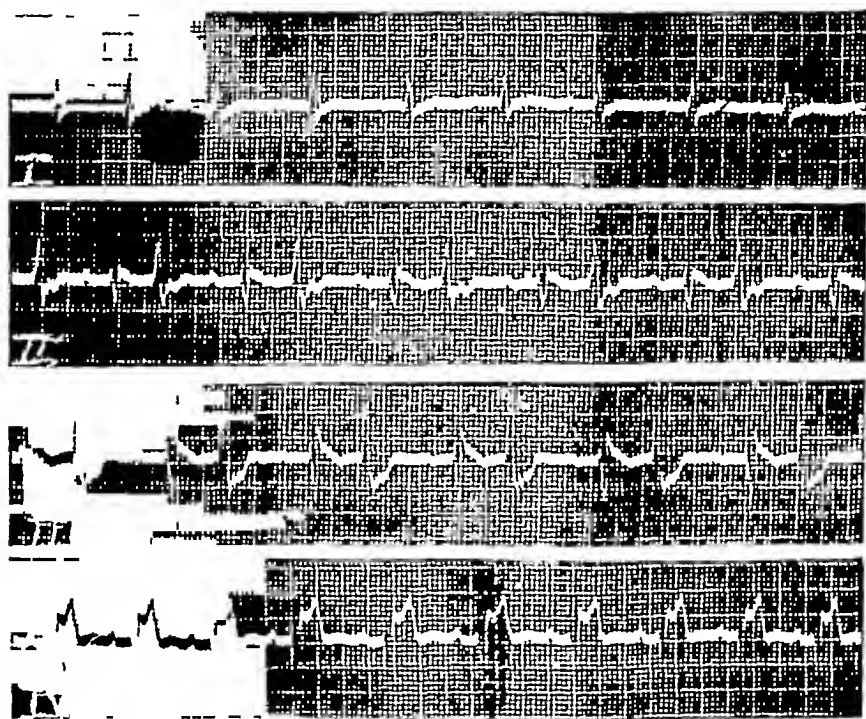


Fig 173—*Digitalis bigeminy*—regularly recurring ventricular premature contractions with P-R interval of 0.24 second in Lead II

reflex origin, or toxic sources, the use of digitalis greatly increases the number and frequency of this arrhythmia. Various general and local anesthetics produce toxic extrasystoles. In certain susceptible individuals tobacco, coffee and alcohol induce ventricular premature contractions. Barium chloride and other drugs may have a similar effect. Allergic states and reactions are frequently accompanied by extrasystoles. The therapy in this group is obvious and the causative factor can frequently be named by the patient from his own experience. The cause can thus be removed.

4 Organic heart disease does commonly present ventricular premature contractions. They are frequently multifocal in origin (Fig

174) Hypertensive, arteriosclerotic, rheumatic and thyrotoxic heart disease as well as acute myocardial infarction have this associated arrhythmia. Premature contractions may be combined with other rhythmic disturbances of the heart or may precede and possibly lead into such serious disturbances of rhythm as ventricular tachycardia or ventricular fibrillation. A note of caution must be interjected in the use of digitalis where ventricular extrasystoles are present in organic

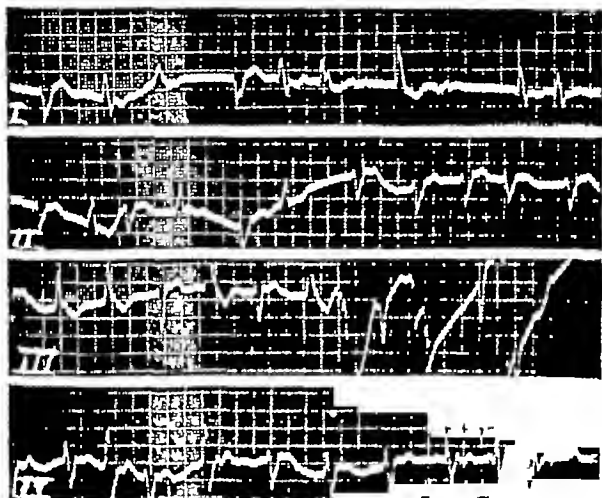


Fig. 171.—Multifocal origin of premature ventricular contractions in severe coronary arteriosclerotic disease. There are several artefacts due to movement which also distort the electrocardiogram. Auricular fibrillation is also present.

heart disease. If the indications for the use of the drug are present extreme care must be exercised in its administration. Congestive heart failure particularly the more chronic form with multifocal ventricular extrasystoles will most often be benefited by the drug. Overdosage may easily produce bigeminy. Ventricular premature contractions by digitalis therapy may increase in frequency and ventricular tachycardia or fibrillation may be induced. Slow rather than rapid digitalization is thus the safer procedure.

#### DIAGNOSIS

The arrhythmic ventricular action may be unnoticed by the patient but in the hypersensitive individual profound subjective sensa



tions and fear may be induced. Heart consciousness and palpitation are frequent complaints. The common forms of extrasystoles occur in the slower cardiac rates, particularly when the patient is at rest. At bedtime, when recumbent with slow cardiac rate, the accentuated venous throb in the jugular veins induced by auricular contraction with the right atrioventricular valve closed adds to the discomfort produced by the premature ventricular contraction. The normal ventricular contraction following the compensatory pause is more forceful because of the longer filling period. Sleep is thus prevented. As the heart rate increases from emotion or exertion, the arrhythmia disappears. This is the reason why extrasystoles are not found in the electrocardiogram taken under the stress of emotional stimuli produced by the experience in the electrocardiographic procedure.

Physical activity or exercise testing also aids in differentiating auricular fibrillation and various forms of heart block. These latter are uninfluenced or aggravated, while extrasystoles disappear. Thus clinical recognition is usually easy where the extrasystoles are infrequent. The premature appearance in the cardiac cycle, the simultaneous auscultation of the heart sounds with pulse palpation, and the compensatory pause readily aid the diagnosis of this arrhythmia. However, the electrocardiogram is often necessary and easily indicates the diagnosis. The pattern is typical, as would be expected from an activity resulting from an abnormal stimulus arising in an abnormal location, transmitted over abnormal pathways. Time relationship, direction of waves, contour of deflections and amplitude are the abnormal changes usually produced. Thus the ventricular complex is bizarre, widened, heightened, occurs prematurely. It is followed immediately by a T wave opposite in direction to the main deflection without an ST interval present. A compensatory period of cardiac electric inactivity usually follows.

CASE II—Mrs. M. H., a 59 year old housewife, has been under medical supervision since November 11, 1943 at which time a diagnosis was made of inactive rheumatic heart disease, mitral stenosis and regurgitation with slight cardiac hypertrophy. There have been no evidences of congestive heart failure all during the relatively frequent visits to the office. She has been able to carry on all her household duties despite knowledge of her rheumatic heart disease for forty years with the usual advice to do only light duties. Four full term pregnancies were included. Dizziness, weakness and palpitation were the original complaints presented. Definite improvement occurred under tonic medication as her weight increased from 109 pounds to 115 pounds. In February 1945 ventricular premature contractions were found as the subjective disturbances of nervousness, insomnia, palpitation and

"neck choking" became the complaint. Relatively infrequently occurring extrasystoles were registered in the electrocardiogram illustrated (Fig. 175). The history dated several months back as to their origin associated with the nervous strain induced by caring for a bedridden seriously ill relative.

*Treatment and Course*—The patient was given the following prescription

℞	
Phenobarbital	1.0
Papaverine Hydrochloride	4.0
Quinidine Sulphate	8.0
Theocalcium	16.0
Mix and divide into capsules No. 60	
Directions: A capsule after breakfast and at bedtime	

The instructions were to return in one month. Complete disappearance of the arrhythmia was noted at the revisit. The capsules were advised only upon retiring. After one month the medication was discontinued. The patient found, however, that under emotional stress or secondary to upper respiratory infections to which she was susceptible, the premature contractions returned. She requested a return to the medication. Under the present arrangements in operation since 1945 she resumes the medication as needed, the extrasystoles being readily controlled by the relatively small dosages included in the compounded prescription.

**CASE III**—E. A., a 44 year old truck driver entered the office September 11, 1944 with a history of heart trouble for six months. This was recognized while undergoing a periodic occupational physical examination. He had been advised to discontinue his occupation. He had no complaints and was able to carry on his heavy physical tasks without any difficulty. The complete inventory of the various systems disclosed no subjective evidence from the inquiry. The past history was also surprisingly negative except for a tonsillectomy at 29 years of age performed because a complaint of back pain.

Physical examination and laboratory studies demonstrated essentially normal findings except for a pronounced arrhythmia of the pulse and heart sounds. The clinical diagnosis of ventricular premature contractions was arrived at only after prolonged auscultation of the heart and palpation of the pulse. This was possible because the pronounced arrhythmia would change to an occasional ventricular premature contraction. The electrocardiogram showed the frequent and various combinations such as bigeminy in Lead II and readily indicated the diagnosis of frequent ventricular premature contractions (Fig. 176). The x-ray of the chest, the basal metabolic rate and the exercise testing all gave normal evidence. The man was told to continue working. As he was a lethargic unemotional type of individual the diagnostic implications in the classification previously outlined did not seem

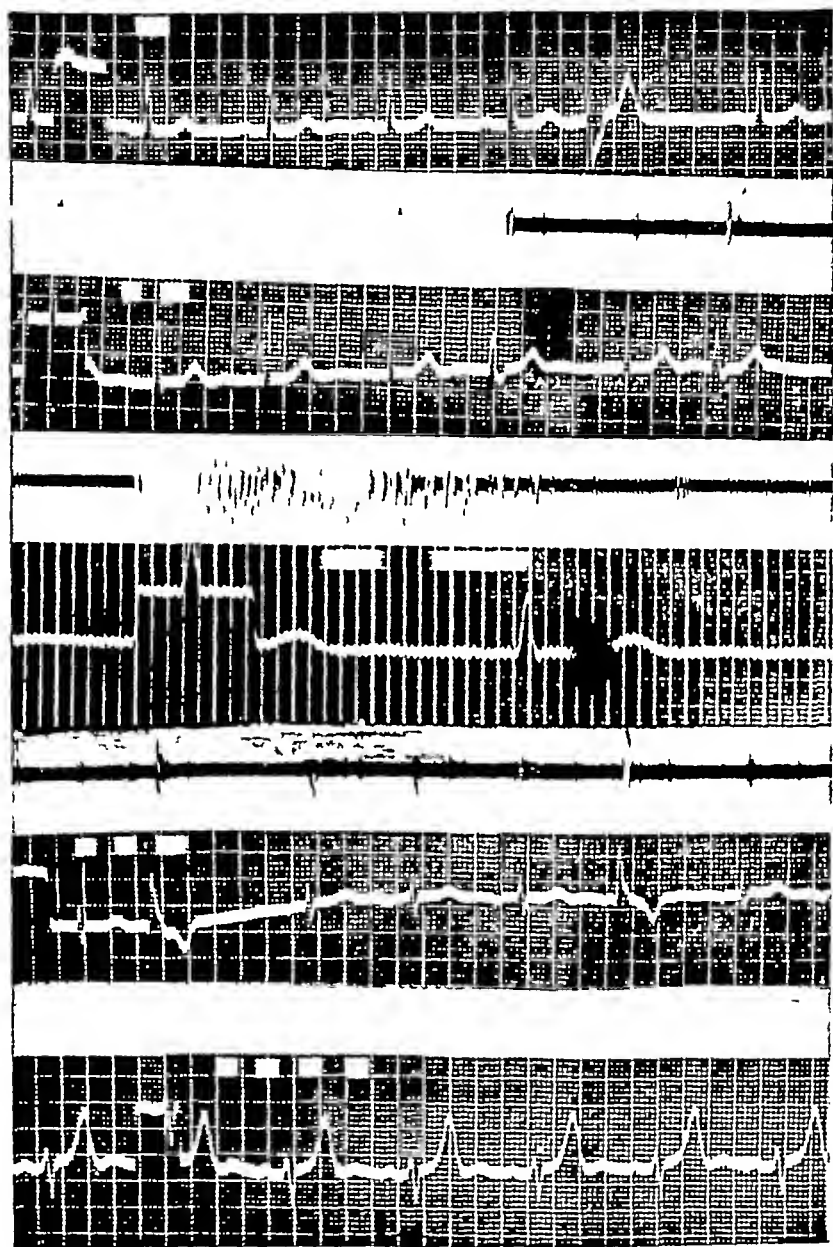
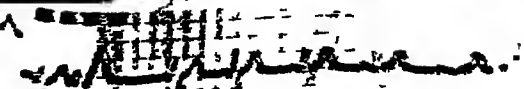
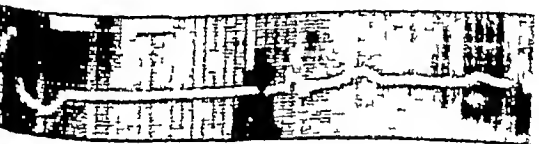


Fig 175—Mrs M H Occasional ventricular premature contractions of left ventricular origin which seriously upset patient but which readily responded to management described



to apply in group I. However reflex, toxic and organic causes likewise were inapplicable.

*Treatment and Course*—The initial therapy in view of the absence of renal disease was as follows

R <sub>x</sub>		
Potassium Acetate		65.0
Syrup of Orange		90.0
Peppermint water to make		240.0
Directions	A teaspoonful in half a glassful of water five times a day	

Diuresis was produced but no effect was noticed on the presence of the extrasystoles. This is the usual response which experience with potassium medication shows. Papaverine hydrochloride in 0.1 gm dosage four times a day was next used. He complained of slight drowsiness but no effect was produced on the arrhythmia. The medication was then changed to quinidine sulfate, capsules 0.2 gm each, to be used starting with one daily and increasing to five a day at three hour intervals. He returned in one week with his arrhythmia uninfluenced but disturbed by the cinchonism produced by the prescription.

Symptomatically the ventricular premature contractions produced no complaints whatsoever. The occupation of the patient was not influenced in any way by the arrhythmia. The challenge to the therapeutic competency of his physician was the principal indication for the continuation of the treatment trials. The diagnosis was apparently of functional origin. Tablets Belladenal Sandoz, one-half tablet before breakfast and supper, were prescribed. There was a great diminution in the frequency of the extrasystoles. The dose was then raised to one tablet after meals and at bedtime, four tablets daily. The arrhythmia disappeared. The therapeutic test indicated the functional etiology of the extrasystoles. The response to this drug, a combination of bellafoline (belladonna alkaloid) with phenobarbital, suggested the response could be either the result of an increase in the heart rate (which was not demonstrated) or more plausibly the following explanation. The extrasystoles were of central origin from the hypothalamic area as Beattie and Brow have demonstrated localization of a focus in the experimental animal. Reduction in dosage to one tablet daily maintained the normal mechanism without return of the ventricular premature contractions.

# A CLINICAL-PATHOLOGICAL STUDY OF THE EFFECT OF SYPHILIS ON THE HEART AND AORTA

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AND

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## SYPHILITIC AORTITIS

Syphilis plays an important etiologic role in the causation of heart disease especially in adult life. It has been reported that up to 90 per cent (Musser<sup>1</sup>) of all patients with latent syphilis have syphilitic aortitis. White<sup>2</sup> found slightly over 50 per cent of cases with positive serology to have syphilitic aortitis. In some parts of the country, especially in the south syphilitic heart disease is estimated to cause as much as 25 per cent of all cardiac disease, with the Negro a frequent victim.

In our experience syphilis does not play such a large role in cardiac disability. The fact that the Negro lives better in the north and is treated earlier may explain the lower incidence of cardiac syphilis in the colored race in this part of the country. The circumstance that rheumatic heart disease is less common in the south than in the north may help to explain this disproportion.

We have had the opportunity at the New York City Hospital to observe a large amount of syphilitic material both in the clinic and at necropsy. This material did not follow the generally accepted pattern as to severity of the clinical course, duration of failure and sudden fatal termination of the disease. In most cases of uncomplicated syphilitic aortitis the disease was latent and the symptoms nil. Many patients lived a normal life span free of cardiac symptoms and died of a totally unrelated disease. It was, therefore, regarded as worth while to review the clinical course and the necropsy findings in 112 cases of syphilitic heart disease.

**Pathology of Cardiovascular Syphilis.**—Syphilis is in essence a productive vascular disease. The vasa vasorum normally penetrate to the outer third or at most to the outer half of the media. The

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intima normally is not vascularized and depends upon diffusion through the endothelium for its nutrition. Infection with syphilis results in a growth of the vasa vasorum through the entire media and extension into the intima, which becomes greatly thickened, producing typical syphilitic plaques. The surface becomes finely or coarsely wrinkled and irregular, due to scattered areas of fibrosis. Connective tissue in the intima invades the aortic ring and often encroaches upon the orifices of the coronary arteries and their extension into the aortic wall. Involvement of the vessel wall beyond the orifices is extremely rare. The syphilitic process usually ends abruptly at the abdominal portion of the aorta. Rupture through the intimal tissue may lead to small dissecting aneurysms in the ascending aorta.

The syphilitic lesion in the aorta may lead to insufficiency of the aortic valves in one of two ways: (1) by widening of the commissures, or (2) by narrowing of the cusps as the result of rolling and thickening of the edges due to extension of the luetic process to the valve. An important contributory factor is focal degeneration of the muscular and elastic layers of the media. Fibrosis of the media develops and the aorta becomes dilated. Destruction of the elastica in the media lowers resistance of the wall of the aorta and may, depending upon the extent of the lesion, lead to saccular or fusiform aneurysms (Carr,<sup>3</sup> Saphir and Scott<sup>4</sup>).

In addition to the syphilitic lesion in the aorta, superimposed arteriosclerosis plays a significant role in the disease. Martland<sup>5</sup> has shown that the chief lesion in acquired syphilis of the aorta is a supravalvular sclerosis and that most of the changes depend upon this lesion. Atheromatous plaques are common in the aorta in the absence of syphilis, but are limited to the intima. Syphilitic infection favors the invasion of fatty material through the vasa vasorum as well as through the intima. Thus syphilis removes one line of defense of the normal aorta against atheromatosis (Leary<sup>6</sup>). It is evident that by this means the frequent and early association of arteriosclerosis with syphilis of the aorta is favored.

Finally, endarteritis of the vasa vasorum may develop and decrease the blood supply to the new vessels in the intima. As a result there is scar formation and necrosis of the intima.

Though syphilis may attack the cardiovascular apparatus in several ways, the lesion most commonly encountered is aortitis and its complications. Spread of the infection takes place by way of the lymphatics. Since the first portion of the aorta is very rich in lymphatics, this part is the common seat of the luetic lesion. Aortitis may be localized

or diffuse and depending upon the area involved there may be associated aneurysm valvular disease or coronary ostial stenosis

For practical purposes cardiovascular syphilis may be classified as follows

### I Aortitis

- (a) Aortitis, uncomplicated (b) aortitis with dilatation of the aorta with or without aneurysm or functional aortic insufficiency (c) aortitis with valvular disease producing aortic insufficiency and (d) aortitis with coronary ostial stenosis.

### II Involvement of myocardium

- (a) Gumma of myocardium (b) myocarditis.

### III Involvement of conduction system producing arrhythmias including heart block

Uncommon types of cardiac syphilis such as gummatous aortitis, localized and diffuse gummatous myocarditis and gummatous aortic valvulus have been reported but are of little clinical significance.<sup>1 2 3 4 5</sup>

### SYPHILITIC AORTITIS WITHOUT VALVULAR DISEASE

**Analysis of Clinical and Postmortem Findings**—This group comprises 34 cases. There were 21 white (16 male 5 female) and 13 Negro (7 male 6 female) patients. The ages varied widely 1 was 30 years old 6 were 40 to 50 all the others were over 50 years of age

It is interesting that the white greatly outnumbered the colored patients, though the Negro population of the City Hospital is high. The lower proportion of Negro to white patients is in interesting contradistinction to that in the south where the proportion of syphilis is much higher among the Negro than among the white population (Musser<sup>1</sup>)

**Pain**—Pain was an important symptom in 12 of 34 patients. It was caused by cardiac infarction in 2 instances with pain lasting one day and three months respectively. In 1 an aneurysm which finally ruptured had caused pain lasting for two months. Marked hypertension and coronary sclerosis had caused pain in 2 of the patients for six years. Acute endocarditis of the aortic valve was found in 1 patient with pain of seven weeks duration. Syphilis of the abdominal aorta was observed in 1 patient with backache lasting six years. Carcinoma of the lung carcinoma of the esophagus, intestinal tuberculosis pulmonary tuberculosis and pneumonia each had caused chest pain in other instances. It is evident that pain was explained by some cause other than syphilis in practically every case except 1 (Table 1)

**Dyspnea**—Dyspnea was a significant complaint in 15 (8 male 7 female) patients. In every case a cause other than uncomplicated a



TABLE 1  
THE ROLE OF SYPHILITIC AORTITIS IN THE CAUSATION OF PAIN

Casc No	Duration	Age	Syphilitic Involvement	Associated Heart Condition	Cause of Death	Heart Weight (gm )
1	1 day	64	Aorta	Acute coronary occlusion Acute cardiac infarct		525
2	3 months	53	Aorta	Acute infarct		800
3	2 months	44	Aneurysm of ascending and descending aorta	Marked coronary sclerosis	Rupture of aneurysm	
4	1 year	30	Ascending aorta		Pulmonary tbc	225
5	3 months	45	Descending aorta with aneurysm		Carcinoma of lung	Normal
6	5 years	47	Entire aorta	Hypertension-246/136 Slight sclerosis of coronary artery	Pulmonary infarction	800
7	1 1/2 months	64	Aneurysm of transverse aorta		Carcinoma of esophagus	Small
8	6 years	66	Abdominal aorta		Carcinoma of bladder	Normal
9	6 years	54	Aorta		Tuberculosis Pulmonary infarction	200
10	?	67	Ascending aorta Narrowing of coronary ostia		Pulmonary tuberculosis	425
11	2 weeks	59	Entire aorta		Broncho-pneumonia	475
12	7 weeks	51	Aorta		Acute endocarditis of aortic valve, pneumonia	500

was found. Nine of the 15 with this symptom had systolic and diastolic hypertension and 2 had systolic hypertension alone. In every case dyspnea was a chronic complaint which could be explained by hypertension which was present or could be assumed from the presence of cardiac hypertrophy. In the patients with dyspnea of more than three months duration the heart weight was 500 gm or more. In the cases without cardiac hypertrophy dyspnea was of extracardiac origin.

Paroxysmal nocturnal dyspnea occurred twice in this group. In 1 patient with aortic insufficiency and essential hypertension the heart weighed 600 gm. The other had had known systolic and diastolic hypertension for twenty years, coronary ostial stenosis and pulmonary tuberculosis.

*Orthopnea*—Orthopnea was a symptom in 3 patients. One had aortic insufficiency, systolic hypertension and an aneurysm; the second had hypertension, narrowing of the coronary ostia and a heart weight of 500 gm; the third had carcinoma of the esophagus and an aneurysm of the transverse portion of the aorta. In 1 case syphilis may have contributed to orthopnea by an ostial stenosis. Since this patient also had marked hypertension and cardiac hypertrophy and dilatation, the relation of syphilis to orthopnea is at best doubtful.

*Heart Failure*—Right heart failure occurred in ten cases. The heart weights ranged from 425 to 800 gm; evidently right heart failure occurred in conjunction with greatly hypertrophied and dilated hearts. Syphilitic aortitis and aneurysms played no role in the causation of failure.

*Cough*—Cough was present in seven cases and was of short duration, lasting from one day to seven months. In one the duration was unknown; in one acute cardiac infarction was the cause. Miliary tuberculosis, bronchiopneumonia, pulmonary infarction, carcinoma of the lung and sepsis each accounted for 1 case of cough which had lasted several weeks. Two of the 7 had aneurysms, one of which ruptured. It is apparent that in 2 instances the cough could have been accounted for by syphilis, though not by uncomplicated luetic aortitis.

*Hoarseness*—Hoarseness was present in 1 instance of an aneurysm with marked dilatation of the ascending aorta and pigskin wrinkling of the entire aorta. There were 6 other cases of syphilitic aneurysm of the aorta, but none of the affected patients had hoarseness.

*Murmurs*—Systolic murmurs were noted at the apex in 7 cases, 2 had associated diastolic murmurs. 1 of these also had a systolic murmur at the aortic area. The finding of a systolic murmur over the area had little significance since all the patients except 3 were over 50 years of age.

*Blood Pressure*—Blood pressure figures were available in 30 cases. There was systolic and diastolic hypertension in 12 patients, 2 had systolic hypertension only, 4 had normal blood pressures with hearts weighing 400 or more gm. In the absence of a valvular lesion, one may assume that these 4 also had had hypertension, making the number with hypertension 16 or possibly 18. Such a large percentage of cases with hypertension might be anticipated since (1) 20 to 25 per cent of the adult population has some degree of hypertension, (2) many of the patients were admitted for associated coronary artery disease, which is often associated with and hastened by hypertension, and (3) a large part of the hospital population is made up of Negroes who have both severe hypertension and arteriosclerotic heart disease.

*Arrhythmias*—There was auricular fibrillation in 2 patients with heart weights of 500 and 800 gm, indicating pre-existing hypertension in the absence of a valvular lesion. Two others had premature beats with pulmonary tuberculosis and pneumonia. A patient with an arrhythmia and heart weight of 700 gm had sepsis. It would appear that syphilitic aortitis with or without aneurysm played no role in the causation of cardiac arrhythmias.

*Electrocardiograms*—Electrocardiograms were available in 16 cases, 1 with a  $Q_2 Q_3$  pattern of acute cardiac infarction, another with auricular fibrillations and intraventricular conduction disturbance and cardiac infarction. Four patients with regular sinus rhythm or left axis shift had small hearts and no cardiac insufficiency, though 1 had coronary ostial narrowing. One with sinus tachycardia and high voltage had a heart weighing 400 gm and no cardiac insufficiency. Eight had left ventricular preponderance, of these, 7 had systolic and diastolic hypertension and 1 with associated left bundle branch block had a heart which weighed 700 gm. Hypertension, cardiac hypertrophy and coronary artery disease accounted for all the abnormal electrocardiograms. Syphilitic aortitis appeared to cause no significant or consistent abnormal pattern in the electrocardiograms.

*Causes of Death*—In those with hypertension, 7 died of cardiac disease. Three of the 7 died of chronic cardiac insufficiency, but none of cardiac syphilis. On the other hand, in the patients without hypertension, none died of cardiac insufficiency, 1 died of rupture of a syphilitic aneurysm. In the 34 cases of syphilitic aortitis only 1 patient died of syphilitic heart disease. The other deaths in chronic cardiac insufficiency were associated with hypertension and cardiac hypertrophy (Table 2).

The relationship of heart weight to heart failure is worthy of comment. In the 9 patients with hearts weighing 200 to 300 gm none had

TABLE 2

CAUSES OF DEATH	No.
Acute cardiac infarction	2
Acute endocarditis	2
Chronic congestive heart failure	3
Rupture of aneurysm	1
Cerebral vascular insult	3
Syphilitic leptomeningitis	1
Brain tumor	1
Pneumonia	4
Pulmonary infarction	2
Pulmonary tuberculosis	3
Miliary tuberculosis	1
Intestinal tuberculosis	1
Peritonitis and pneumonia	1
Hemorrhage from peptic ulcer	1
Nephrosclerosis	1
Pyelonephrosis	1
Carcinoma of the lung	1
Carcinoma of the esophagus	1
Carcinoma of the bladder	1
Carcinoma of the vulva	1
Arsenical poisoning	1
Unknown	1
Total	34

cardiac insufficiency or failure. In the 2 patients with hearts weighing 301 to 400 gm. 1 had had chronic heart failure. Of the 6 patients with hearts weighing 401 to 500 gm. 3 had had left and 2 had had right heart failure. Of the 4 cases with hearts weighing 501 to 600 gm. 2 had right and left failure and death was due to congestive failure in 1. The heart weighing from 601 to 700 gm. and the 2 weighing 701 to 800 gm. had been in failure. Two hearts weighed over 800 gm., but 1 was weighed with an aneurysm. 1 of the 2 cases was in failure. Failure was due to hypertension which had caused marked hypertrophy and dilatation of the heart. Syphilitic aortitis did not cause congestive failure (Table 3).

*Coronary Artery Disease*—Ostial stenosis was present in 5 cases. In 1 of these syphilis was clearly the cause. In the other 4 it could not be determined whether syphilis, arteriosclerosis or both played a part.

*Aorta*—Dilatation of the aorta was observed 10 times. Of the 10 patients 6 had hypertension, judging by the actual figures or by the heart weights. The ages varied from 46 to 67 years and 6 were under 50 years. Of these 6, 2 had hypertension leaving 4 patients aged 41 to 62 with dilatation of the aorta and normal blood pressures. At these ages dilatation may be due to syphilis as well as to arteriosclerosis of the aorta in the absence of hypertension or valvular disease.

TABLE 3  
RELATION OF HEART WEIGHT TO CONGESTIVE FAILURE

Heart Weight (gm )	Number	Number in Failure
200-300	9	0
301-400	2	1
401-500	6	3
501-600	4	2
601-700	1	1
701-800	2	2
801 plus	2	1
Not stated	8	3

Five without hypertension or failure

*"Tree-barking"* of the aorta was recorded in 28 of the 34 cases. The others had aneurysms or ostial stenosis or a cellular reaction in the intima and adventitia with endarteritis and fenestration of the aortic valves. Sites of *"tree-barking"* of the aorta were the ascending portion in 13 (in 3 of these it was present in the suprasedgmental portion with pearly plaque formation), in the entire aorta in 4, in the ascending aorta in 1, in the descending portion in 1, in the abdominal aorta in 1, location not given in 7.

*Aneurysms* were observed in 7, and at the following sites: in the arch and descending portion in 1, in the ascending arch and descending portion in 1, in the transverse portion in 1, in the descending portion in 1, in the ascending and transverse portions with compression of pulmonary artery in 1, in the thoracic portion with thrombosis in 1, and multiple of the arch in 1.

#### SYPHILITIC AORTITIS WITH VALVULAR DISEASE

**Analysis of Clinical Findings**—There were 53 cases, 32 white patients, 20 Negro, 1 whose race was not recorded. Nine were females, of whom 5 were white and 4 were Negro. Of the 44 male patients, 27 were white and 16 were Negro. As in the first group, there was a preponderance of white over Negro patients, reaching a proportion of 2 to 1.

*Pain in the chest* was an important symptom in 16 instances, *in the abdomen* in 1. There was more than one possible factor besides aortitis responsible for pain. These were (1) coronary arteriosclerosis, (2) marked cardiac enlargement, (3) congestive failure, (4) acute myocarditis of rheumatic or infectious origin. Pain in seven cases possibly was luetic in origin. In 3 of the 7, pain was due to aneurysms,



TABLE 4

PAIN IN THE PATIENTS WITH LEUTIC AORTIC INSUFFICIENCY

Case No	Duration	Blood Pressure	Coronary Arteries	Heart Weight (gm)	Cause of Death
1	—	190/110		320	Acute miliary tuberculosis
2	3 years	185/110	Moderate sclerosis	350	Carcinoma of stomach, bronchopneumonia
3	Long duration	180/70	Coronary sclerosis	500	Rupture of aneurysm
4	3 months	170/60	Occlusion right coronary ostium, coronary sclerosis	660	Syphilis of aortic valve
5	4 months	145/20	Ostial stenosis, right and left	950	Acute myocarditis
6	Several hours	120/40			
7	1 1/2 months	128/52	Right coronary artery atresia	460	Acute infectious endocarditis of aortic valve, miliary infarcts
8	1 month	190/120		800	Perforation of aneurysm into stomach
9	3 months	105/40		375	Pneumonia
10	16 months	204/100	Coronary sclerosis	875	Cardiac failure
11	4 years	148/100	Coronary sclerosis	1250	Acute cardiac infarction
12	3 months			300	Bronchopneumonia
13	2 years	110/70	Coronary sclerosis	975	Rupture of right ventricle
14	9 months	100/48	Coronary stenosis, right and left	625	Lobar pneumonia
15	1 month			700	Acute infectious myocarditis, pneumonia
16	9 months	122/65		300	Acute pericarditis, pneumonia

remaining 14 with normal diastolic blood pressures had aortic insufficiency. Of the remaining 10 cases with normal systolic and diastolic blood pressures none had clinical aortic insufficiency. However an elevated or normal diastolic blood pressure is consistent with the presence of well-established aortic insufficiency.

Dyspnea was an important complaint in 34 cases. Every one had anatomical aortic valvular disease which may have been a possible factor in the causation of this symptom. In addition 8 had marked systolic and diastolic hypertension and 9 had systolic hypertension alone. Of the 8 cases with systolic and diastolic hypertension all except 2 had greatly hypertrophied hearts which weighed over 510 gm., indicating marked hypertrophy. The 2 hearts without marked cardiac hypertrophy weighed 400 and 460 gm. and were from cases of debilitating diseases—carcinoma and tuberculosis, which may have lessened or prevented cardiac hypertrophy, all had right and left heart failure except two.

The 9 patients in the group with systolic hypertension alone had hypertrophied hearts with the exception of 1 which weighed 250 gm. 6 of the 9 had right and left, 2 had left failure only and 1 had no cardiac failure.

Paroxysmal nocturnal dyspnea was encountered 4 times in this group. In 3 the weights were known and were between 500 and 875 gm. All had greatly hypertrophied hearts and were in congestive failure. The association of congestive failure with significant cardiac hypertrophy is well established as is seen in Table 5.

TABLE 5

TABLE OF HEART WEIGHTS AND CONGESTIVE HEART FAILURE

Heart Weight (gm.)	Number	Number in Failure
201-300	6	3 (2 of the 3 were acute)
301-400	13	7
401-500	9	6
501-600	5	3
601-700	10	10
701-800	2	2
801-900	1	1
901 plus	3	3
Not stated	4	3

Arrhythmias occurred in 10 cases. Auricular fibrillation was found in 2 cases of hypertensive heart disease. Bigeminal and trigeminal pulse was noted in 1 patient with aortic insufficiency. Tachycardia was ob-



served twice, in a hypertensive patient with bronchial asthma, and in a patient with aortic insufficiency. Gallop rhythm was recorded 3 times—in 1 patient with aortic insufficiency, acute infectious endocarditis and left heart failure, in another with bilateral pneumonia, and in a third one with right and left heart failure secondary to hypertension. An arrhythmia of undetermined type was associated with aortic insufficiency, acute cardiac damage and pneumonia. Bradycardia with a rate of 27 occurred in a patient with right and left heart failure and bronchopneumonia.

*Electrocardiograms* were available in 27 cases. The tracings were normal in 2. In one of these the blood pressure was 150/80, and the heart was small, the second had a gallop rhythm, left heart failure, aortic insufficiency, and a blood pressure of 128/52. Left axis deviation was observed in 4 cases. Three of the 4 had hypertension, the fourth had aortic insufficiency, the hearts were hypertrophied in 3, and in the fourth the heart weight was 350 gm. Left ventricular strain was found in 16 cases. All except 1 had significant cardiac hypertrophy, the 1 without hypertrophy had systolic and diastolic hypertension, 185/110, a malignant tumor of the stomach, and the heart weighed 350 gm. Of the 16, 10 had aortic insufficiency, 6 had systolic and diastolic hypertension, 3 had systolic hypertension only. Right ventricular strain occurred in a patient with gallop rhythm and right heart failure, and at necropsy the heart weighed 400 gm.

Negative T waves occurred with a heart weight of 500 gm, commissural syphilis, coronary sclerosis and congestive failure. Left bundle branch block with premature ventricular beats was found in a greatly enlarged heart weighing 1250 gm in association with right heart failure and hypertension. Low voltage was observed in a case of acute pericarditis, pneumonia and congestive heart failure, the heart weighed only 350 gm.

*Coronary Artery Disease*—In 24 cases there were varying degrees of coronary arteriosclerosis. Ostial stenosis was present in 12 cases. In 5 the lesion was limited to the right coronary artery, in 6 there was involvement of both coronary arteries, and in 1 the site was not recorded. The ages of the patients with this condition varied from 35 to 75 years. Four had associated coronary arteriosclerosis, which was, however, minimal in 1.

*Valves*—All the valves showed commissural syphilis with separation of the cusps. The lesions in the valves were: commissural separation, 53, thickening of aortic valves, 13, fenestration of aortic valves, 5, rolling of aortic valves, 8, fusion of aortic valves, 1. Atheromatous changes: sclerosis of mitral valves, 6, sclerosis of aortic valves, 2 (cal-

ified at the base in 1 with aneurysm of commissure in 1) thickening separation and fenestration, 1 and separation and fenestration 5

*Aorta*—There was widening of the aorta in 26 cases widening with aneurysms occurred in 13 cases The aneurysms occurred in the base in 3, in the entire aorta in 2 in the entire thoracic portion in 1 in the arch and descending portions in 5 and in 2 the site of the lesion was not stated Dilatation of the aorta was most marked in the arch and the descending portions of the aorta.

Wrinkling (tree-barking) was described in 50 of 58 cases The sites of involvement of the aorta by this lesion were in the proximal portion in 23 in the ascending portion of the arch in 3 in the entire arch in 1, in the descending portion of the aorta in 1 in both the thoracic and abdominal portions of the aorta in 3 in the entire thoracic aorta in 5 and in the abdominal aorta in 1 The sites of involvement were not stated in 11

*Causes of Death*—There were 22 deaths due to heart disease In a large number of these hypertension and not syphilis was the cause In two instances rupture of a syphilitic aneurysm caused death Nineteen died a noncardiac death (Table 6)

TABLE 6  
CAUSES OF DEATH IN VALVULAR CASES

<i>Cardiac</i>	Number
Acute cardiac infarction	1
Rupture of right ventricle	1
Pericarditis	2
Acute myocarditis	3
Acute infectious endocarditis	6
Rheumatic heart disease and luetic aortic insufficiency	1
Congestive failure	3
Hypertensive	2
Syphilitic	1
Uremia	2
Rupture of aneurysm	
<i>Noncardiac</i>	
Carcinomas	6
Brain tumors	2
Hemiplegias	2
Meningitis	1
Cirrhosis of liver	1
Tuberculosis	2
Pulmonary	2
Miliary	2
Pulmonary embolism	1
Cystitis	11
Pneumonia	1
Not stated	

TABLE 7  
CHEST PAIN IN DISPENSARY GROUP

Color	Age	Sex	Duration	Valve Lesion	Blood Pressure
B	54	M	8 years	Aortic insufficiency	170/80, 170/50, 206/60
B	54	M	27 years	Aortic insufficiency, aneurysm of arch	210/130
W	50 +	M	8 years	Aortic insufficiency, aneurysm of ascending aorta	108/30
W	58	M	1 year	Aortic insufficiency, dilated arch, enlarged left ventricle	230/110
B	51	M	1 year +	Aortic insufficiency, dilatation of ascending aorta	140/30, 165/36
B	53	M	1 year	No valve lesion, dilated aorta	210/110
W	59	M	Unknown	No valve lesion	204/110
B	61	M	4 1/2 years	Aortic insufficiency, dilatation of ascending aorta	210/110
B	55	M	Unknown	Aortic insufficiency	190/70, 175/60
B	?	M	3 1/2 years	Aortic insufficiency, dilatation of ascending aorta	110/25
B	30	M	9 months	Aortic insufficiency, aorta en- larged to right and left	104/70
W	53	M	4 years	No valve lesion, no enlargement of heart	170/120
B	60	M	?	No valve lesion, dilated aorta	180/110
B	63	M	7 years	Aortic insufficiency, aneurysm of ascending aorta	200/65



TABLE 8

## EXERTIONAL DYSPNEA IN DISPENSARY GROUP

(Showing relation of dyspnea to blood pressure, heart size and failure)

Color	Age	Sex	Duration	Blood Pressure	Failure
B	61	M	4 1/2 years	210/110	Right and left failure
B	—	M	3 1/2 years	110/25	
B	52	M	5 years	140/50	Heart enlarged, right and left failure
B	68	M	5 years	134/80	Heart enlarged, right and left failure
W	54	M	8 years	210/130	Heart enlarged, no failure
B	54	M	8 years	170/80 206/50	Heart enlarged, right failure 3 years, left failure 8 years
W	50 +	M	8 years	130/38	Heart enlarged, right and left failure 8 years
B	63	M	9 years	200/65	Heart enlarged, right failure
W	53	M	4 years	170/120	
B	46	F	2 years	120/80	
W	58	M	1 year	220/110	Heart enlarged, right failure
B	51	M	3 months	140/30	Heart enlarged
B	53	M	1 year	210/110	Heart enlarged
W	59	M	3 years	204/110	Heart enlarged, right and left failure
B	55	M	1 year	190/70	Heart enlarged
B	46	M	16 months	166/104	Heart enlarged, right heart failure 1 year
W	65	M	3 months	—	Heart enlarged, acute failure, re- sponse to treatment
B	69	M	11 months	180/90	Heart enlarged, acute failure 11 months before examination
B	74	M	1 year	170/70	Heart enlarged

pressure. All 4 had considerable enlargement of the heart and a history of failure, or were in congestive failure. In 3 there was also electrocardiographic evidence of left ventricular preponderance or damage of the anterior wall of the left ventricle.

*Cough* was an important complaint in 6 patients lasting from one to four and a half years. The heart was enlarged in all these patients. Four had aortic insufficiency and dilatation of the aorta, 1 with an aneurysm. Five of the 6 had right and left heart failure.

*Aneurysms*—Aneurysms were observed 7 times, in the arch in 1, in the ascending portion of the aorta in 4 (in 1 of these another aneurysm in the descending portion of the arch), in the innominate artery in 1 and in the right carotid artery in 1. All 7 cases had associated aortic insufficiency.

*Right or Left or Combined Ventricular Failure*

	Left	Right
Up to 1 year	6	5
1-2 years	5	3
2-3 "	1	2
3-4 "	1	2
4-5 "	3	
Over 5 "	4	
Unknown		2

No congestive failure was present in 5 cases.

*Electrocardiograms*—One or more electrocardiograms was available in 23 of the 25 cases. There was sinus rhythm and left axis deviation respectively in 2 cases of aortic insufficiency. Left ventricular preponderance was present in 17. Twelve of the 17 had aortic insufficiency; of these 12, 4 also had essential hypertension and three had systolic hypertension only. Four of the 17 had cardiac infarction. 2 of the anterior and 2 of the posterior wall of the left ventricle. 1 had right axis deviation with left ventricular preponderance, aortic insufficiency and right and left ventricular failure.

### COMMENT

*Age, Sex and Race*—The great majority of the patients constituting over 50 per cent of all three groups, were between 51 and 70 years of age. Only 11 per cent of the patients with valvular disease and 9 per cent of those without valvular disease were 40 years of age or younger. In the group followed in the clinic, 1 was less than 40 years of age. Comparison between syphilitic and rheumatic cardiac disease shows that rheumatic heart disease starts in the first and second decades and that 52.2 per cent of the patients with aortic disease and 69 per cent of those with mitral valvular disease have died before the

age of 40 (Coombs<sup>12</sup> and White<sup>13</sup>) The cardiac manifestations of syphilis usually develop in the fourth and fifth decades and frequently persist into the sixth decade Hypertension may begin in the fourth decade, may make its effects manifest especially in the fifth and sixth decades, and frequently later especially in female patients It is evident that syphilitic heart disease does not manifest itself early, or run a short course

Analysis of the role of sex shows that there were 90 males and 22 females, making a ratio of about 4 to 1, similar to the findings of other observers<sup>14</sup>

The racial predisposition of Negroes to syphilis has received much attention in the literature In the south where there is a large Negro population with syphilis the incidence of cardiac syphilis is high among Negroes Musser<sup>1</sup> reports that 25 per cent of cardiac disease in the south is syphilitic Figures for the proportion of cardiac syphilis vary in different parts of the country, from 5 to 25 per cent<sup>15 16 17</sup>

In this material there was more cardiovascular syphilis among white than among Negro patients, in the proportion of 58 to 53 In the outpatient department of the hospital where the population is overwhelmingly Negro, the number of syphilitic patients was greater among Negro patients However, it appears that race is not a predisposing factor in cardiovascular syphilis

The serology had limited value In 16 patients (14 per cent) of the entire series the blood Wassermann or Kahn reaction was negative This finding corresponds to the reports in the literature In view of this fact the diagnosis should be made if there are other findings suggestive of syphilis

**Pain**—Of the 112 patients 34 had cardiac pain Since many of the patients had more than one cause for anginal pain, it was not possible to determine the exact cause in any case In 10 there was postmortem evidence of the syphilitic origin of the pain, in the 14 clinic cases 3 had aneurysms with cardiac pain Of the remaining 10, 6 had hypertension, 2 of the 6 had no valvular disease, the other 4 had valvular disease Five had luetic aortic valvular disease In 4 there was cardiac infarction, 2 in the anterior and 2 in the posterior wall It appears that in at least 13 patients and perhaps in a considerable additional number, syphilitic vascular disease probably accounted for anginal pain

Contrary to the findings of Musser,<sup>1</sup> our experience has been that Negroes frequently complain of anginal pain In a group of 25 clinic patients, 10 of 14 with this complaint were Negroes A strong predilection to develop pain was observed in the male sex (Arkin<sup>16</sup>), whether syphilitic or arteriosclerotic heart disease was the cause Though nu

merous observers have reported the occurrence of substernal pain in uncomplicated syphilitic aortitis<sup>14, 15, 20</sup> in this material there was no case of precordial pain due to uncomplicated aortitis

**Dyspnea**—This complaint was an important feature in 15 patients with aortitis without valvular disease. In each instance dyspnea was a chronic complaint. In every one there were either hypertensive blood pressure figures or there was cardiac hypertrophy to indicate previous hypertension. This fact holds for the cases with orthopnea and paroxysmal nocturnal dyspnea as well. Aneurysms like aortitis did not appear to cause dyspnea. Ostial stenosis may have been a contributory factor to dyspnea in one case. Of the 53 patients with valvular disease 34 had dyspnea but all had aortic insufficiency. 8 of these had marked systolic and diastolic hypertension. 9 had systolic hypertension alone. All except 3 had marked cardiac hypertrophy. Of the clinic group of 25, 19 complained of dyspnea and cardiac hypertrophy was demonstrable in practically all. The single constant finding in this material as in the work of others who studied cardiac insufficiency in syphilitic and nonsyphilitic heart disease was the presence of considerable cardiac hypertrophy.<sup>21, 22, 23, 24</sup>

**Blood Pressure**.—In the 34 cases of syphilitic aortitis cardiac enlargement and insufficiency were due in every instance to hypertension. In the group of 53 with aortic valvular syphilis hypertension was frequently an associated finding. In this group it was noteworthy how frequently normal systolic and diastolic blood pressure figures were associated with aortic insufficiency. In exceptional instances severe aortic valvular incompetence occurred with marked diastolic hypertension. However commissural syphilis with anatomical aortic insufficiency is compatible with normal circulatory dynamics and may produce no clinical evidence of aortic incompetence.

Systolic hypertension is a compensatory phenomenon to compensate for inadequate coronary flow during diastole in aortic insufficiency (Cregg<sup>25</sup>). Whether in this material systolic hypertension is compensatory or a remnant of essential hypertension in which the diastolic blood pressure was lowered by marked aortic valve incompetence is impossible to state. Only the presence of hypertensive retinopathy or renal insufficiency would establish previous essential hypertension in a patient with aortic insufficiency who shows systolic but no diastolic hypertension.

**Electrocardiograms**.—In the group without aortic insufficiency the findings were either those of a shift in axis, cardiac infarction or ventricular strain due to cardiac enlargement. In those with aortic insufficiency the findings included sinus rhythm, left axis shift, low voltage,



bundle branch block, and most commonly left ventricular strain in the presence of a considerably enlarged heart. It is seen that the electrocardiogram was determined by the underlying ventricular strain or myocardial damage, and that syphilis causes no specific electrocardiogram. Klotz and Crede<sup>28</sup> observed that T wave negativity encountered in early syphilis, indicative of coronary insufficiency, disappears after intensive anti-syphilitic treatment.

**Cardiac Insufficiency**—In every case of congestive failure, a valvular lesion or hypertension was responsible for this condition. Aortitis did not cause cardiac insufficiency, nor did aortitis cause coronary insufficiency unless coronary flow was impeded by ostial stenosis. Ostial stenosis caused acute coronary and cardiac insufficiency in the same way as coronary arteriosclerosis.

Chronic coronary insufficiency due to any cause rarely causes chronic congestive heart failure in the absence of hypertension or valvular disease. The most significant finding in chronic cardiac insufficiency and failure is marked increase in heart weight<sup>27, 22</sup>. Though chronic cardiac insufficiency is rare in small hearts, it is common in hearts weighing 500 or more grams (Nathanson<sup>28</sup>). The average heart weight in syphilitic heart failure has been found to be about 555 gm. by Reid,<sup>28</sup> 620 gm. by Clawson and Bell<sup>21</sup> and 642 gm. by Scott.<sup>29</sup> The average weight of the hearts of our cases with luetic aortitis without failure was 329 gm., and in the cases of failure 557 gm. In the hearts with aortic insufficiency without failure the average heart weight was 357 gm., and in those with failure 598 gm. Evidently in syphilitic aortic insufficiency the dynamics governing the development of cardiac insufficiency are the same as in nonluetic heart disease. The greatly enlarged heart which is unable to undergo further hypertrophy develops additional dilatation which is, however, no longer a stimulus for additional hypertrophy. Failure is then chronic and usually progressive.

Many cases followed the usually accepted course of a severe, short period of failure lasting less than two years. The reason for this course was (1) the extensive destructive valvular damage, and (2) the resulting marked cardiac hypertrophy and dilatation, with hearts at necropsy weighing 600 to 900 or more grams.

In many instances, however, the patients suffered from hypertensive and syphilitic heart disease, and were similar to a group studied by Royster, Lisa and Carroll.<sup>30</sup> Nevertheless, though the heart suffered from a double burden, failure recurred over a period lasting several years. In some cases congestive failure repeatedly lessened, and the patient stayed well for years. It is necessary to conclude that syphilitic aortic insufficiency may follow a slow course of valvular destruction,

is not extensive and only slowly progressive. In such cases, even with the added burden of associated hypertension, the clinical course may be that of hypertensive rather than syphilitic heart disease. In these patients progress of the two diseases may be slower than that of aortic insufficiency alone associated with rapid valvular destruction. The view that failure in aortic insufficiency lasting longer than two years is not syphilitic is erroneous. The duration of failure depends upon the speed of destruction of the aortic valves and not upon etiology.

The frequent occurrence of sudden death in cardiac disease is well known. The presence of ostial stenosis in such cases in syphilitic heart disease is equally well established. Saphir and Scott<sup>4</sup> found ostial stenosis in 88 per cent of their cases. Sudden death occurs also in non-syphilitic valvular disease, myocarditis and coronary artery disease. As Weiss<sup>21</sup> pointed out, there is probably a common denominator in sudden death in all types of heart disease, namely autonomic nervous system imbalance, since acute anatomical changes in the heart are often not found at necropsy. In this material there were examples of ostial stenosis, but this condition did not cause sudden death in any.

#### DIAGNOSIS AND COURSE OF SYPHILITIC AORTITIS

The diagnosis of syphilitic aortitis is difficult to make. According to Maynard<sup>22</sup> the diagnosis is possible in life in only 2.5 per cent of cases.

The criteria given in the literature for the diagnosis of uncomplicated syphilitic aortitis are: (1) the demonstration of a dilated aorta by x-ray or fluoroscopy or increase in retromanubrial dullness; (2) increase in density of the aorta; (3) episternal pulsation, particularly in a patient under forty years of age in the absence of hypertension; (4) a systolic murmur over the aortic area; (5) accentuation of the aortic second sound, often described as bell like in the absence of hypertension and arteriosclerosis; (6) a history of chancre or a positive Wassermann reaction; (7) exertional or paroxysmal dyspnea or an abrupt onset of circulatory embarrassment; (8) absence of mitral valvular disease; and (9) hypertension. Each of these points deserves additional comment.

1. Dilatation of the aorta shown by x-ray or percussion as an increase in retromanubrial dullness may be of diagnostic value, but this finding has meaning only in the absence of a valve lesion, hypertension and diffuse arteriosclerosis, since in these conditions dilatation of the aorta is very common. Schwedel<sup>23</sup> examined 30,000 army and navy recruits and found that 5 per cent of healthy men between the ages of 17 and 37 had some dilatation of the aorta in the absence of hyperten-

sion or valvular disease. On the other hand, 30 per cent of luetic subjects had dilatation of the aorta. Since both normal and syphilitic individuals have dilatation of the aorta, the diagnosis of luetic aortitis can only be presumptive.

2 Increased density of the aorta may be due to syphilis or arteriosclerosis or both, since atheromatous changes are frequently superimposed on luetic lesions, according to Martland.<sup>5</sup> The finding of isolated aortic sclerosis is, therefore, of diagnostic value of syphilis only in young persons under 40, without hypertension or premature arteriosclerosis.

3 Episternal pulsation due to elongation of the aorta may, like increased density of the aorta, also be due to syphilis, hypertension or arteriosclerosis. The observation of episternal pulsation must, therefore, be evaluated in the same way as increased density of the aorta.

4 A systolic murmur over the aortic area is usually due to dilatation of the aorta or to roughening of its wall. Such a murmur occurs frequently in persons over 40, and in many conditions such as hypertension, arteriosclerosis and anemia. The murmur in this material was conspicuous by its rarity. However, such a murmur in a younger person without hypertension or cardiac disease, especially when associated with accentuation of the aortic second sound, should lead one to suspect aortic syphilis. This view is also held by Woodruff.<sup>34</sup>

5 Accentuation of the aortic second sound occurs under the same conditions as the systolic murmur over the aortic area, and its diagnostic value is subject to the same limitations. Description of the aortic second sound as bell-like is subject to personal vagaries. Such a sound was not encountered in this material.

6 A history of chancre or a positive Wassermann reaction has value in the diagnosis of syphilis of the aorta only if there are other indisputable evidences for the diagnosis. It is well to remember that even in patients with syphilis, dilatation of the aorta need not be due to this cause.

7 An abrupt onset of cardiac insufficiency is looked upon as typical of uncomplicated luetic aortitis. We encountered no instance in which this condition accounted for cardiac insufficiency. In every instance another cause such as hypertension or valvular disease was found complicating the aortitis.

8 Absence of a mitral valvular lesion has been regarded as an additional criterion in favor of a diagnosis of luetic aortitis. The absence of such a valve defect is significant only in the case of an aortic insufficiency appearing suddenly in middle life and known from previous observation to have been absent.

9 The development of hypertension has been looked upon as an other finding suggestive of syphilitic aortitis. Hypertension is a common finding in middle life when luetic heart disease is usually manifest but there is no reason to believe that the two diseases are causally related

Carter and Baker<sup>25</sup> enumerated the above mentioned criteria for the diagnosis of cardiovascular syphilis. Subsequently many authors misquoted them as having stated that their criteria referred to uncomplicated syphilitic aortitis. From a physiologic point of view it is evident that if aortitis has not extended to the coronary ostia and has not resulted in an aneurysm which produces pressure it is not reasonable to expect symptoms no matter where the site of involvement nor how extensive such involvement is. This view is in keeping with the absence of findings of circulatory embarrassment, cardiac failure and paroxysmal dyspnea in this material in uncomplicated syphilitic aortitis. Wilson<sup>26</sup> also felt that uncomplicated luetic aortitis is of purely anatomical interest. Silverman and Dressler<sup>27</sup> state that syphilitic aortitis is the most easily overlooked visceral type of syphilis. It is difficult then to see how they diagnosed 24 per cent of uncomplicated syphilitic aortitis. They stress the importance of the bell like quality of the aortic second sound which in our opinion is open to much imagination on the part of the examiner.

Aneurysm of the aorta occurs by an extension of the syphilitic process into the wall of the aorta. Depending upon the part of the aorta involved there is an aneurysm of symptoms or of signs. The aneurysm of signs is usually situated in the anterior chest and though impressive in size is relatively symptomless. The aneurysm of symptoms on the other hand may be smaller but on account of its site produces symptoms such as cough, hoarseness, dysphagia, backache and dyspnea. An aneurysm situated above the aortic ring which does not cause aortic insufficiency by dilatation of the ring does not cause cardiac enlargement or insufficiency. Marland<sup>2</sup> and Bourne<sup>28</sup> made similar observations. The diagnosis of an aneurysm which does not produce symptoms or signs can only be established by x ray or fluoroscopy.

A difficult problem is the diagnosis of aortic stenosis. The condition develops by an extension of the syphilitic lesion to the mouth of the coronary arteries and may produce typical coronary insufficiency such as effort syndrome or coronary thrombosis in the same way as coronary arteriosclerosis. The differential diagnosis of the two conditions is therefore very difficult. Both may come on suddenly, both occur in middle adult life, both are induced by effort and both produce cardiac

infarction and similar electrocardiographic changes. Rest may produce benefit in both. However, marked improvement in angina of effort on antiluetic therapy carefully administered, especially if the patient is known to have syphilis and the aorta is widened and dense, suggests ostial stenosis. In coronary arteriosclerosis a period of rest in bed may cause considerable and even permanent improvement. Bed rest alone, however, would at most cause temporary improvement in ostial stenosis, since the disease is a chronic and progressive one. Subsequent improvement on antisiphilitic treatment would favor the diagnosis of ostial stenosis.

**Aortic Insufficiency**—In the 25 clinic cases of cardiovascular syphilis, aortic insufficiency was present in 18. Of the 53 patients with aortic valvular syphilis who came to necropsy, only 15 had aortic diastolic murmurs. The small number of patients with murmurs in the necropsy material is impressive. This discrepancy can best be explained by the fact that the clinic patients were all chosen because they had frank aortic or valvular syphilis. The necropsy material, on the other hand, embraced all cases of anatomical aortic valvular disease, of these only a few showed aortic insufficiency in life. Evidently anatomical syphilitic aortic valvular disease is not always sufficiently advanced to be of clinical significance.

Thompson<sup>18</sup> found the murmur of aortic insufficiency to be very soft and almost inaudible, and at the left sternal border in early aortic insufficiency, but over the sternum at the 2nd and 3rd interspaces or to the right of the sternum when more marked. Possibly minimal commissural involvement caused no murmurs, or murmurs that were so faint as to be inaudible.

Some clinicians contend that aortic insufficiency of syphilitic origin can be differentiated from that of rheumatic heart disease by the site of the murmur. The murmur to the right of the sternum is regarded as syphilitic, whereas the murmur to the left of the sternum is supposedly rheumatic (Garvin<sup>17</sup>). We believe that the site of the murmur depends upon the position of the aortic valve in relation to the chest wall, and that the site of the murmur is valueless as a point in differential diagnosis. The murmur will be heard on the right side when the valve is close to the right side of the chest, and will be propagated to the left side of the chest when the valve is in close proximity to the left side of the chest. The site of the murmur does not permit any conclusion as to etiology.

Of greater significance than site in establishing syphilis as the cause of an aortic diastolic murmur, is the appearance of such a murmur in a person of 35 to 50 who for the preceding five or ten years was known

to have had no aortic diastolic murmur. Opinion is strengthened if the patient has no hypertension if he has a positive Wassermann reaction or is known to have had syphilis.

The uncommon case of an isolated rheumatic aortic insufficiency may offer difficulty. However, the murmur does not appear suddenly in a rheumatic subject and is usually known to have existed for a long time. The presence of aortic stenosis alone or in combination with other murmurs excludes syphilis. Accentuation of the apical first and the pulmonic second sound, enlargement of the left auricle, the pulmonary artery segment or both, point to rheumatic heart disease. Atrial fibrillation usually occurs in rheumatic patients and is rare in syphilis.

Aortic insufficiency secondary to hypertension or arteriosclerosis offers a relatively small problem. The patient is usually in the older age group. The murmur is due to organic changes that occur in the aortic valves with the formation of a sclerotic bicomate lesion and thickening of the midportion of the free edges of the valves (Gouley and Sickel<sup>24</sup>). The murmur is rarely very loud, is usually localized and transmitted over a small area. The systolic and diastolic elevation of the blood pressure is maintained. The aortic second sound is loud despite the murmur. The peripheral signs of aortic insufficiency are usually not marked.

The aortic diastolic murmur of severe anemia is due to stretching of the aortic ring (Goldstein and Boas<sup>25</sup>). It is not loud or widely transmitted and disappears with improvement of the blood status.

#### SUMMARY AND CONCLUSIONS

1. A series of 112 cases of cardiovascular syphilis was analyzed. Twenty five were observed in a dispensary; 87 were studied from necropsy protocols. Of the 87, 53 had aortic valvular involvement and 34 had luetic aortitis without valvular disease.

2. Uncomplicated syphilitic aortitis is an interesting anatomical entity but a symptomless disease. The diagnosis of uncomplicated syphilitic aortitis in persons over 40, especially in the presence of arteriosclerosis or associated hypertension, is very difficult to make. Even in young persons without hypertension or syphilis the diagnosis is difficult since 5 per cent of normal young people have dilatation of the aorta. A systolic murmur over the aortic area is of no value in the differential diagnosis in persons over 40 years of age. The bell-like aortic second sound did not occur in this material. Uncomplicated syphilitic aortitis did not cause cardiac insufficiency or anginal pain. In every one

of the 34 cases of syphilitic aortitis, symptoms including cardiac enlargement or insufficiency were due to other causes

3 Aneurysms complicating syphilitic aortitis produce signs and symptoms only in so far as they cause pressure phenomena Cardiac enlargement and failure do not occur except when the aneurysm causes a relative aortic insufficiency by proximity to the aortic valves

4 Ostial stenosis occurred seventeen times and caused coronary insufficiency by compromising the coronary arteries in the same way as coronary arteriosclerosis In no instance was the condition responsible for sudden death in this material

5 In the group with valvular disease pain was present in almost one third of the patients and was due to several causes, chiefly non-syphilitic, such as coronary arteriosclerosis In 7 cases pain was due to syphilis, in 3 to ostial stenosis, and in 4 to aneurysms

6 Dyspnea was a symptom in 34 of 53 cases with aortic insufficiency In every one of these there was also considerable cardiac hypertrophy due to aortic insufficiency or some other cause Congestive failure was associated with marked cardiac hypertrophy and was common in hearts weighing 500 or more grams as in nonsyphilitic heart disease

7 Aortic commissural syphilis occurred in many instances without clinical aortic insufficiency

8 Aortic insufficiency may be regarded as syphilitic by exclusion When due to hypertension the murmur is localized and of short duration, the diastolic blood pressure is high and the aortic second sound is accentuated Aortic insufficiency due to rheumatic heart disease is usually of long duration and often associated with disease of the mitral valve Frequently there is a history of rheumatic fever A diastolic aortic murmur appearing suddenly in middle adult life and previously known to have been absent is usually syphilitic A history of syphilis and a positive Wassermann reaction help in establishing the diagnosis The site of the murmur is of no etiologic significance and is heard to the right or the left of the sternum, depending upon the degree of rotation of the heart and the position of the aortic valves in relation to the chest wall

9 Many patients followed a short rapid course with aortic insufficiency apparently due to rapid severe destruction of the aortic valves Others, however, recovered repeatedly from episodes of congestive failure over a number of years The variations were due to the rapidity or slowness with which aortic valvular disease progressed

10 The electrocardiogram was of no help in the diagnosis of cardiac syphilis, muscle damage, ventricular strain and patterns of cardiac infarction occurred as in nonsyphilitic cardiac disease

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